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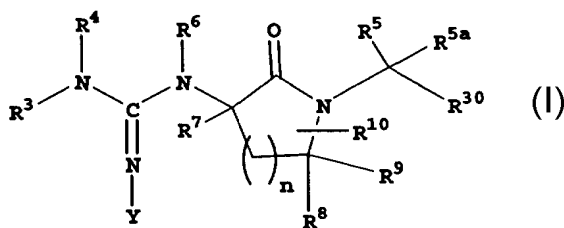
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(54) Title: LACTAM INHIBITORS OF FACTOR XA WHICH ARE USEFUL FOR THE TREATMENT OF THROMBOSIS



(57) Abstract: Compound of the formula (I) are inhibitors of the enzyme Factor Xa. These compounds are useful as anticoagulants in the treatment of cardiovascular diseases associated with thromboses.

LACTAM INHIBITORS OF FACTOR XA WHICH ARE USEFUL FOR THE TREATMENT OF THROMBOSIS

This application claims priority to provisional U.S. Application No. 60/222,498 filed August 2, 2000, the
5 entirety of which is incorporated herein by reference.

Field of the Invention

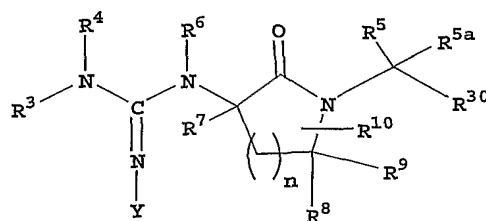
The present invention relates to lactam inhibitors
10 of the enzyme Factor Xa which are useful as
anticoagulants in the treatment of cardiovascular
diseases associated with thromboses.

Brief Description of the Invention

15

In accordance with the present invention, novel lactam derivatives are provided which are inhibitors of the enzyme Factor Xa and have the structure I

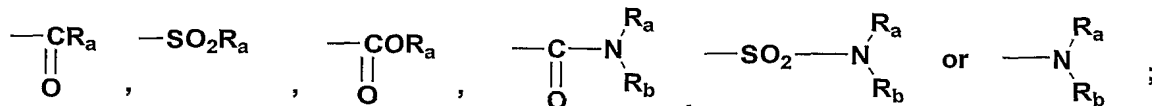
(I)



20 including pharmaceutically acceptable salts thereof and all stereoisomers thereof, and prodrugs thereof, wherein

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n is an integer from 1 to 5;
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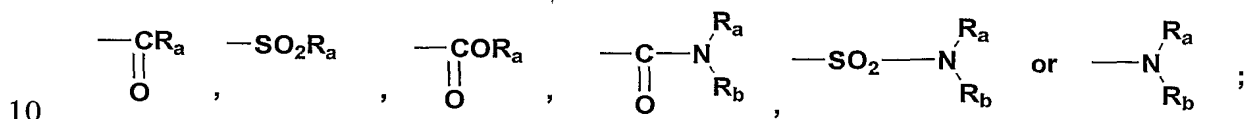
25 Y is selected from hydrogen, alkyl, substituted
alkyl, alkenyl, substituted alkenyl, alkynyl, substituted
alkynyl, aryl, cycloalkyl, heteroaryl, cycloheteroalkyl,
cyano, nitro, hydroxy, amino, -OR_a, -SR_a,



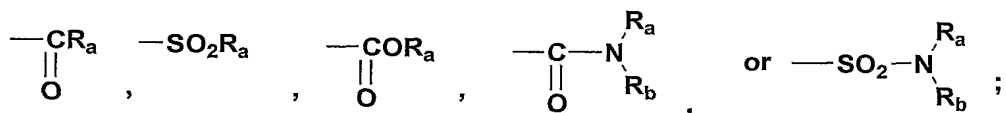
30 R⁴, R⁶, R⁸, and R⁹ are the same or different and
are independently selected from hydrogen, alkyl,

substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl, cycloheteroalkyl, cycloalkyl, alkylcarbonyl, arylcarbonyl, cycloalkylcarbonyl, substituted alkyl-carbonyl, cycloheteroalkylcarbonyl and heteroarylcarbonyl;

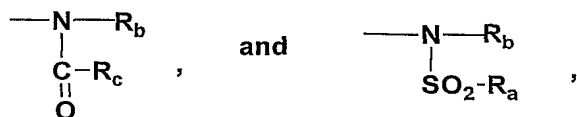
R^3 is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl, cycloalkyl, cycloheteroalkyl, cyano, nitro, hydroxy, $-OR_a$, $-SR_a$,



R^5 , R^{5a} , and R^7 are the same or different and are independently selected from hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, heteroaryl, cycloalkyl, aryl, cycloheteroalkyl,

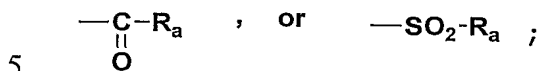


R^{10} is selected from hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl, cycloalkyl, alkylcarbonyl, arylcarbonyl, cycloheteroalkyl, cycloalkylcarbonyl, substituted alkyl-carbonyl, cycloheteroalkylcarbonyl, heteroarylcarbonyl,



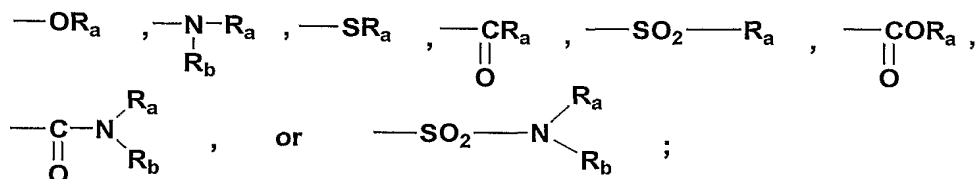
or when R^9 is hydrogen and R^8 and R^{10} are on adjacent carbons they join to complete a cycloalkyl or phenyl ring;

R^{30} is alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, heteroaryl, cycloalkyl, aryl, cycloheteroalkyl,



R_a and R_b are the same or different and are independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl, cycloheteroalkyl, cycloalkyl, 10 alkylcarbonyl, arylcarbonyl, cycloalkylcarbonyl, substituted alkyl-carbonyl, cycloheteroalkylcarbonyl, heteroarylcarbonyl, aminocarbonyl, alkylaminocarbonyl and dialkylaminocarbonyl;

R_c is hydrogen, halogen, alkyl, substituted alkyl, 15 alkenyl, substituted alkenyl, aryl, heteroaryl, cycloalkyl, cycloheteroaryl,



20 and wherein R^3 and R^4 and/or R_a and R_b can be taken together with the nitrogen to which they are attached,

i.e. $\text{—}\overset{\text{R}_a}{\underset{\text{R}_b}{\text{N}}}$, to form a cycloheteroalkyl ring or a heteroaryl ring;

R^3 and Y can be taken together to form a 25 heteroaryl ring;

R^3 or R^4 or Y can form a ring with R^6 which can be a cycloheteroalkyl or a heteroaryl ring;

R^5 and R^{5a} can be taken together to the carbon to which they are attached to form a cycloalkyl ring, a 30 heteroaryl ring or a cycloheteroalkyl ring; and

where one or more of R^3 R^4 or R^6 are H, then double bond isomers are possible which are included in the present invention.

In addition, in accordance with the present
5 invention, a method for preventing, inhibiting or
treating cardiovascular diseases associated with
thromboses is provided, wherein a compound of formula I
is administered in a therapeutically effective amount
which inhibits Factor Xa.

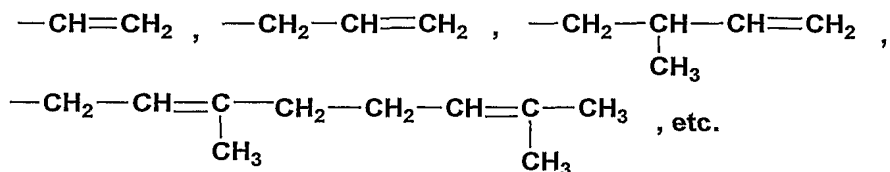
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Detailed Description of the Invention

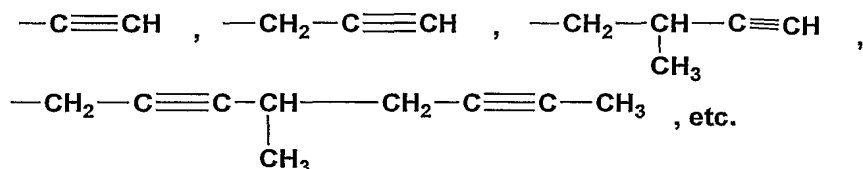
The following definitions apply to the terms as
used throughout this specification, unless otherwise
15 limited in specific instances.

The term "alkyl" or "alk" as employed herein alone
or as part of another group includes both straight and
branched chain hydrocarbons containing 1 to 20 carbons,
preferably 1 to 12 carbons, more preferably 1 to 8
20 carbons in the normal chain. Examples include methyl,
ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl,
pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl,
octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl,
dodecyl, and the various additional branched chain
25 isomers thereof. The term "lower alkyl" includes both
straight and branched chain hydrocarbons containing 1 to
4 carbons.

The term "alkenyl" as employed herein alone or as
part of another group includes both straight and branched
30 hydrocarbons having one or more double bonds, preferably
one or two, and being of 2 to 20 carbons, preferably 2 to
12 carbons, and more preferably 2 to 8 carbons in the
normal chain. Examples include



The term "alkynyl" as employed herein alone or as part of another group includes both straight and branched hydrocarbons having one or more triple bonds, preferably one or two, and being of 2 to 20 carbons, preferably 2 to 12 carbons, and more preferably 2 to 8 carbons in the normal chain. Examples include

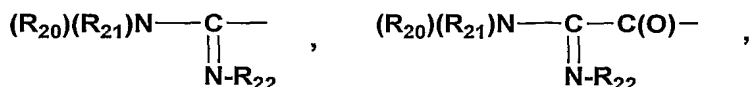


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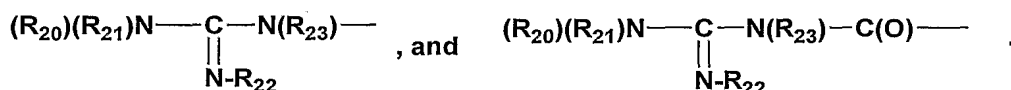
The terms "substituted alkyl", "substituted lower alkyl", "substituted alkenyl" and "substituted alkynyl" refer to such groups as defined above having one, two, or three substituents selected from halo, alkoxy, haloalkoxy, cycloalkyl, cycloheteroalkyl, aryl, heteroaryl, arylcycloalkyl, aryloxy, arylalkoxy, heteroaryloxy, hydroxy, $-\text{N}_3$, nitro, cyano, $(\text{R}_{20})(\text{R}_{21})\text{N}-$, carboxy, thio, alkylthio, arylthio, arylalkylthio, heteroarylthio, alkyl-C(O)-, alkoxycarbonyl, $(\text{R}_{20})(\text{R}_{21})\text{N}-\text{C}(\text{O})-$, arylcarbonyloxy, alkyl-C(O)-NH-, alkyl-C(O)-N(alkyl)-, aryl-C(O)-NH-, aryl-C(O)-N(alkyl)-, aryl-C(O)-, arylalkoxycarbonyl, alkoxycarbonyl-NH-, alkoxycarbonyl-N(alkyl)-, cycloalkyl-C(O)-, cycloheteroalkyl-C(O)-, heteroaryl-C(O)-, cycloalkyl-C(O)-NH-, cycloalkyl-C(O)-N(alkyl), cycloheteroalkyl-C(O)-NH-, cycloheteroalkyl-C(O)-N(alkyl)-, heteroaryl-C(O)-NH-, heteroaryl-C(O)-N(alkyl)-, arylsulfinyl, alkylsulfinyl, cycloalkylsulfinyl, cycloheteroalkylsulfinyl, heteroarylsulfinyl, arylsulfonyl, alkylsulfonyl, cycloalkylsulfonyl,

30

cycloheteroalkylsulfonyl, heteroarylsulfonyl, $(R_{20})(R_{21})N$ -sulfinyl, $(R_{20})(R_{21})N$ -sulfonyl, alkyl-SO₂-NH-, alkyl-SO₂-N(alkyl)-, aryl-SO₂-NH-, aryl-SO₂-N(alkyl)-, cycloalkyl-SO₂-NH-, cycloalkyl-SO₂-N(alkyl)-, cycloheteroalkyl-SO₂-NH-,
 5 cycloheteroalkyl-SO₂-N(alkyl)-, heteroaryl-SO₂-NH-, heteroaryl-SO₂-N(alkyl)-, $(R_{20})(R_{21})N$ -C(O)-NH-, $(R_{20})(R_{21})N$ -C(O)-N(alkyl)-, hydroxy-NH-C(O)-, hydroxy-N(alkyl)-C(O)-,



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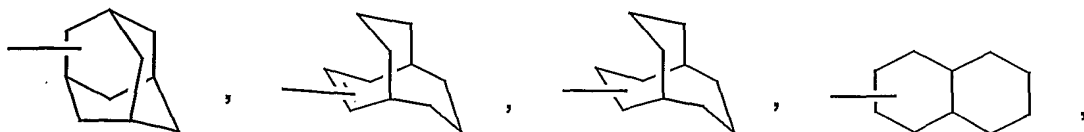


The term "halo" refers to chloro, bromo, fluoro and iodo.

15

The term "cycloalkyl" as employed herein alone or as part of another group includes saturated or partially unsaturated (containing 1 or 2 double bonds and/or 1 or 2 triple bonds) cyclic hydrocarbon groups containing 1 to 3 rings, including monocyclicalkyl, bicyclicalkyl and
 20 tricyclicalkyl, containing a total of 3 to 20 carbons forming the rings, preferably 4 to 12 carbons forming the rings. Also included within the definition of "cycloalkyl" are such rings fused to an aryl, cycloheteroalkyl, or heteroaryl ring and bridged
 25 multicyclic rings containing 5 to 20 carbons, preferably 6 to 12 carbons, and 1 or 2 bridges. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl, cyclohexenyl,

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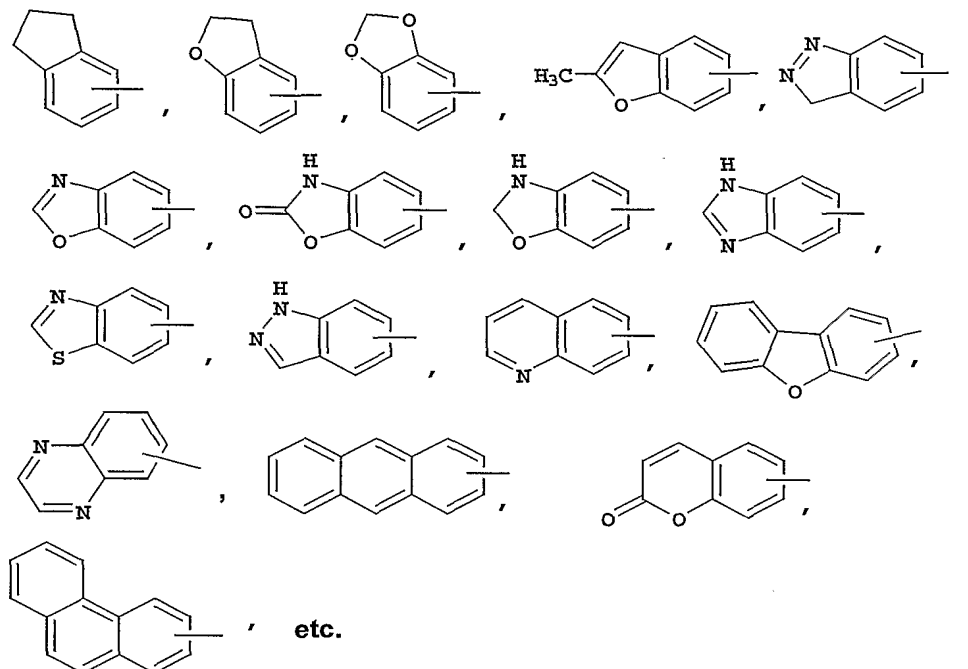


cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclohexadienyl, cycloheptadienyl, cyclopentynyl, cyclohexynyl, cycloheptynyl, cyclooctynyl, etc. Also

included within the definition of "cycloalkyl" are such groups having one, two or three substituents selected from alkyl, substituted alkyl, halo, hydroxy, $(R_{20})(R_{21})N-$, alkoxycarbonyl, alkoxy, aryl, aryloxy, arylthio, heteroaryl and cycloheteroalkyl.

The term "aryl" as employed herein alone or as part of another group refers to phenyl, 1-naphthyl, and 2-naphthyl as well as such rings fused to a cycloalkyl, aryl, cycloheteroalkyl, or heteroaryl ring.

Examples include



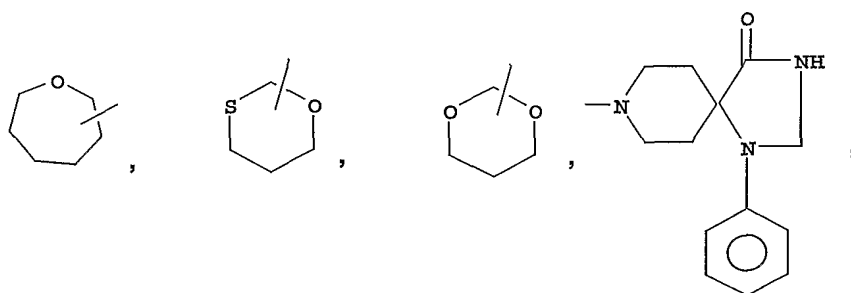
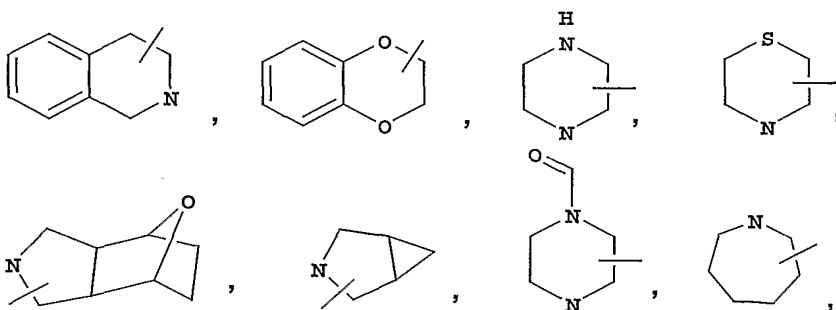
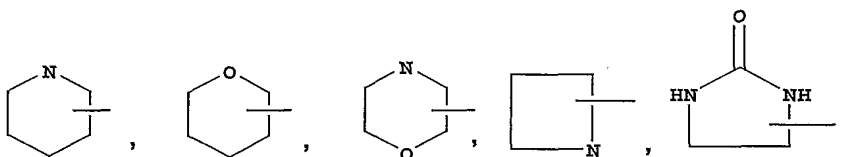
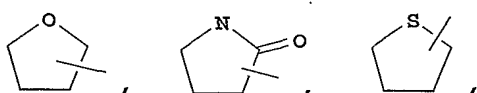
The term "aryl" also includes such ring systems wherein the phenyl, 1-naphthyl, or 2-naphthyl has one two, or three substituents selected from halo, hydroxy, alkyl, alkenyl, alkoxy, haloalkoxy, carboxy, cyano, nitro, substituted alkyl, substituted alkenyl, alkylcarbonyl, (substituted alkyl) $-C(O)-$, aryloxy, arylalkoxy, arylthio, arylalkylthio, cycloheteroalkyl, heteroaryl, $-N(R_{20})(R_{21})$, alkyl- SO_2- , (substituted alkyl)- SO_2- , aryl- SO_2- , cycloalkyl- SO_2- , cycloheteroalkyl- SO_2- , heteroaryl- SO_2- , alkyl- SO_2-NH- , aryl- SO_2-NH- , cycloheteroalkyl- SO_2-NH- , heteroaryl- SO_2-NH- , alkyl- SO_2-

N(alkyl)-, (substituted alkyl)-SO₂-N(alkyl)-, cycloalkyl-SO₂-N(alkyl)-, aryl-SO₂-N(alkyl)-, cycloheteroalkyl-SO₂-N(alkyl)-, heteroaryl-SO₂-N(alkyl)-, (R₂₀) (R₂₁)N-C(O)-, (R₂₀) (R₂₁)N-C(O)-NH-, aryl-C(O)-, cycloalkyl-C(O)-, cycloheteroalkyl-C(O)-, heteroaryl-C(O)-, alkyl-O-C(O)-, substituted alkyl-O-C(O)-, cycloalkyl-O-C(O)-, aryl-O-C(O)-, heteroaryl-O-C(O)-, cycloheteroalkyl-O-C(O)-, alkyl-SO₂-O-, substituted alkyl-SO₂-O-, cycloalkyl-SO₂-O-, aryl-SO₂-O-, heteroaryl-SO₂-O-, cycloheteroalkyl-SO₂-O-, (R₂₀) (R₂₁)-N-SO₂-O-, (R₂₀) (R₂₁)-N-SO₂-, (R₂₀) (R₂₁)N-C(O)-N(alkyl)-,

$$\text{H}_2\text{N}-\underset{\text{NH}}{\underset{\parallel}{\text{C}}}-\text{NH}-\text{C}(\text{O})-$$
 , HO-NH-C(O)-, HO-N(alkyl)-C(O)-, formyl, HC(O)-NH-, arylalkoxycarbonyl-NH-C(O)-, arylalkoxycarbonyl-N(alkyl)-C(O)-, (R₂₀) (R₂₁)N-C(O)-alkyl-NH-C(O)-, (R₂₀) (R₂₁)N-C(O)-alkyl-N(alkyl)-C(O)-, aryl-C(O)-NH-SO₂-, aryl-C(O)-N(alkyl)-SO₂-, cycloalkyl-C(O)-NH-SO₂-, cycloalkyl-C(O)-N(alkyl)-SO₂-, heteroaryl-C(O)-NH-SO₂-, cycloheteroalkyl-C(O)-NH-SO₂-, heteroaryl-C(O)-N(alkyl)-SO₂-, cycloheteroalkyl-C(O)-N(alkyl)-SO₂-, alkyl-C(O)-NH-SO₂-, alkyl-C(O)-N(alkyl)-SO₂-, substituted alkyl-C(O)-NH-SO₂-, substituted alkyl-C(O)-N(alkyl)-SO₂-, (R₂₀) (R₂₁)N-C(O)-alkyl-NH-C(O)-alkyl-NH-C(O)-, (R₂₀) (R₂₁)N-C(O)-alkyl-N(alkyl)-C(O)-alkyl-NH-C(O)-, and (R₂₀) (R₂₁)N-C(O)-alkyl-NH-C(O)-alkyl-N(alkyl)-C(O)-, as well as pentafluorophenyl. Phenyl and substituted phenyl are the preferred aryl groups.

The term "cycloheteroalkyl" as used herein alone or as part of another group refers to 3-, 4-, 5-, 6- or 7-membered saturated or partially unsaturated rings which includes 1 to 2 hetero atoms such as nitrogen, oxygen and/or sulfur, linked through a carbon atom or an available nitrogen atom. Also included within the definition of cycloheteroalkyl are such rings fused to a cycloalkyl or aryl ring and spiro cycloheteroalkyl rings. One, two, or three available carbon or nitrogen atoms in

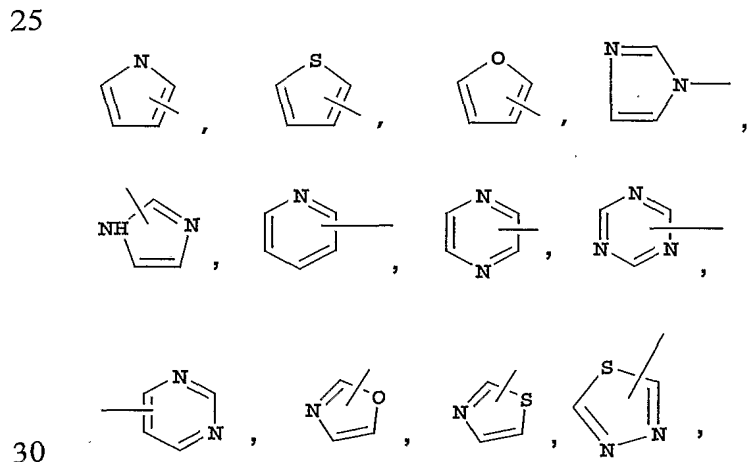
the cycloheteroalkyl ring can be substituted with an alkyl, substituted alkyl, $(R_{20})(R_{21})N-$, aryl, cycloalkyl, keto, alkoxycarbonyl, arylalkoxycarbonyl, alkoxycarbonyl-NH-, alkoxycarbonyl-N(alkyl)-, arylalkoxycarbonyl-NH-
5 arylalkoxycarbonyl-N(alkyl)-, alkylcarbonyl-NH-, alkylcarbonyl-N(alkyl)-, arylcarbonyl, alkylsulfonyl, arylsulfonyl, substituted alkylsulfonyl, $HO-N=$, alkoxy- $N=$, $(O)CH-$, or $(R_{20})(R_{21})N-C(O)-$. Also, an available nitrogen or sulfur atom in the cycloheteroalkyl ring can
10 be oxidized. Examples of cycloheteroalkyl rings include

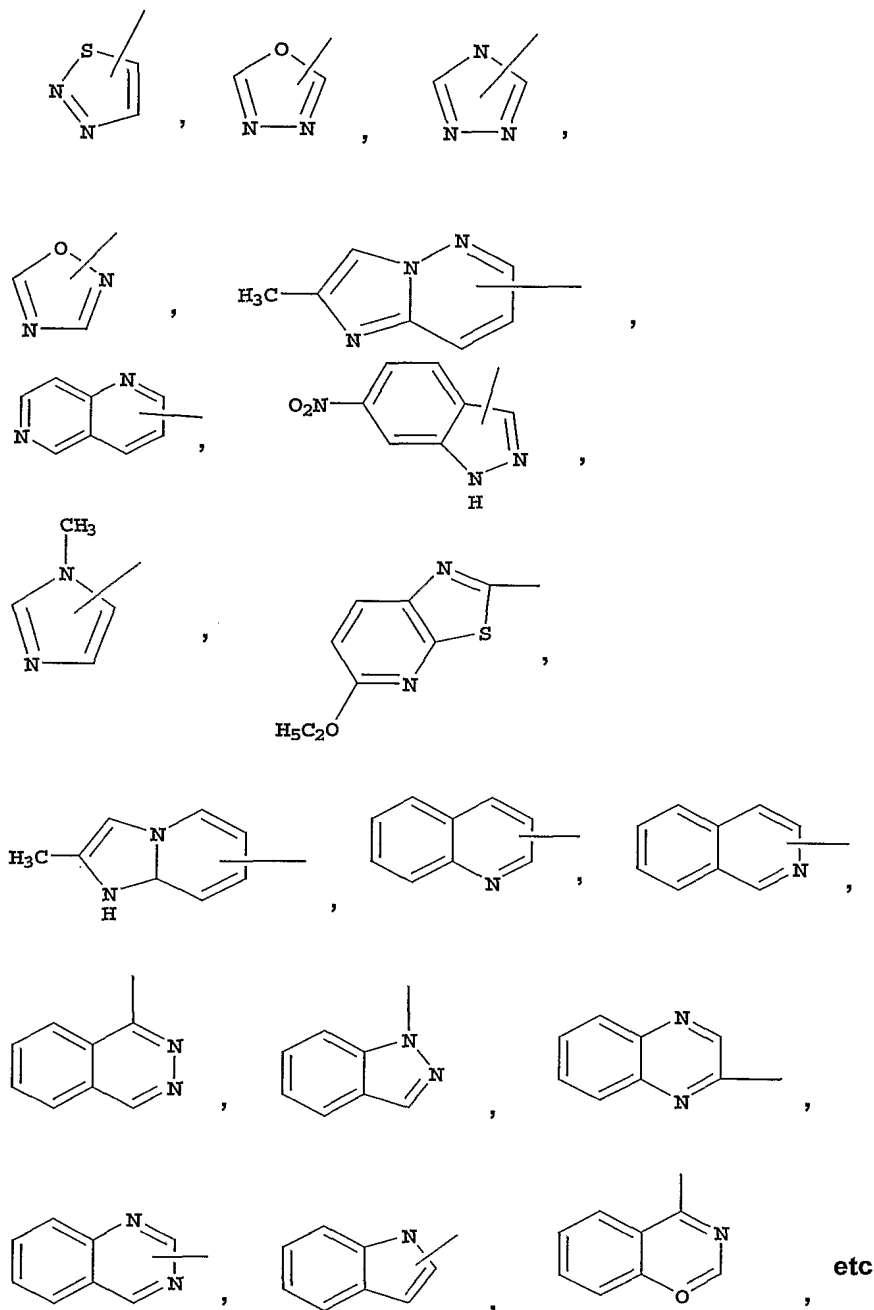


20 etc. Depending on the point of attachment, a hydrogen
may be missing from the nitrogen atom in the above rings.

The term "heteroaryl" as used herein alone or as part of another group refers to a 5- 6- or 7- membered aromatic

rings containing from 1 to 4 nitrogen atoms and/or 1 or 2 oxygen or sulfur atoms provided that the ring contains at least 1 carbon atom and no more than 4 heteroatoms. The heteroaryl ring is linked through an available carbon or nitrogen atom. Also included within the definition of heteroaryl are such rings fused to a cycloalkyl, aryl, cycloheteroalkyl, or another heteroaryl ring. One, two, or three available carbon or nitrogen atoms in the heteroaryl ring can be substituted with an alkyl, substituted alkyl, alkoxy, alkylthio, keto, halo, hydroxy, cycloalkyl, aryl, cycloheteroalkyl, heteroaryl, $(R_{20})(R_{21})N-$, nitro, carboxy, cyano, alkoxycarbonyl, aryloxy carbonyl, alkylcarbonyl, substituted alkyl-C(O)-, arylcarbonyl, cycloalkylcarbonyl, $(R_{20})(R_{21})N-C(O)-$, guanidinylcarbonyl, $(R_{20})(R_{21})N-C(O)-alkyl-$, $NH-C(O)-$, $(R_{20})(R_{21})N-C(O)-alkyl-N(alkyl)-C(O)-$, $alkyl-C(O)-NH-$, $alkyl-C(O)-N(alkyl)-$, substituted alkyl-C(O)-NH-, substituted alkyl-C(O)-N(alkyl)-, cycloalkyl-C(O)-NH-, cycloalkyl-C(O)-N(alkyl)-, aryl-C(O)-NH-, aryl-C(O)-N(alkyl)-, heteroaryl-C(O)-NH-, heteroaryl-C(O)-N(alkyl)-, cycloheteroalkyl-C(O)-NH-, cycloheteroalkyl-C(O)-N(alkyl)-, alkyl-SO₂-, substituted alkyl-SO₂-, aryl-SO₂-, cycloalkyl-SO₂-, cycloheteroalkyl-SO₂-, or heteroaryl-SO₂. Also an available nitrogen or sulfur atom in the heteroaryl ring can be oxidized. Examples of heteroaryl rings include





10 Again, depending on the point of attachment, a hydrogen may be missing from the nitrogen atom in the above rings.

The term "alkoxy" as employed herein alone or as part of another group includes "alkyl" groups as defined above bonded to an oxygen. Similarly, the term

15 "alkylthio" as employed herein above or as part of

another group includes "alkyl" groups as defined above bonded to a sulfur.

R_{20} , R_{21} , R_{22} and R_{23} are the same or different and are independently selected from hydrogen, alkyl,
5 substituted alkyl, cycloalkyl, aryl, cycloheteroalkyl and heteroaryl.

The compounds of formula I can be prepared as salts, in particular pharmaceutically acceptable salts. If the compounds of formula I have, for example, at least
10 one basic center, they can form acid addition salts. These are formed, for example, with strong inorganic acids, such as mineral acids, for example sulfuric acid, phosphoric acid or a hydrohalic acid, with strong organic carboxylic acids, such as alkanecarboxylic acids of 1 to
15 4 carbon atoms which are unsubstituted or substituted, for example, by halogen, for example acetic acid, with saturated or unsaturated dicarboxylic acids, for example oxalic, malonic, succinic, maleic, fumaric, phthalic or terephthalic acid, with hydroxycarboxylic acids, for
20 example ascorbic, glycolic, lactic, malic, tartaric or citric acid, with amino acids, (for example aspartic or glutamic acid or lysine or arginine), or benzoic acid, or with organic sulfonic acids, such as (C_1 - C_4)-alkyl- or aryl-sulfonic acids which are unsubstituted or
25 substituted, for example by halogen, for example methane- or p-toluene sulfonic acid. Corresponding acid addition salts can also be formed if the compounds of formula I have an additional basic center. The compounds of formula I having at least one acid group (for example
30 COOH) can also form salts with bases. Suitable salts with bases are, for example, metal salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts, or salts with ammonia or an organic amine, such as morpholine, thiomorpholine,
35 piperidine, pyrrolidine, a mono-, di- or tri-lower alkylamine, for example ethyl-, tert-butyl-, diethyl-, diisopropyl-, triethyl-, tributyl- or dimethyl-

propylamine, or a mono-, di- or trihydroxy lower
alkylamine, for example mono-, di- or triethanolamine.
Corresponding internal salts may furthermore be formed.
Salts which are unsuitable for pharmaceutical uses but
5 which can be employed, for example, for the isolation or
purification of free compounds I or their
pharmaceutically acceptable salts, are also included.

Preferred salts of the compounds of formula I
include monohydrochloride, hydrogensulfate,
10 methanesulfonate, phosphate or nitrate.

All stereoisomers of the compounds of the instant
invention are contemplated, either in admixture or in
pure or substantially pure form. The compounds of the
present invention can have asymmetric centers at any of
15 the carbon atoms including any one of the R substituents.
Consequently, compounds of formula I can exist in
enantiomeric or diastereomeric forms or in mixtures
thereof. The processes for preparation can utilize
racemates, enantiomers or diastereomers as starting
20 materials. When enantiomeric or diastereomeric products
are prepared, they can be separated by conventional
methods for example, chromatographic or fractional
crystallization.

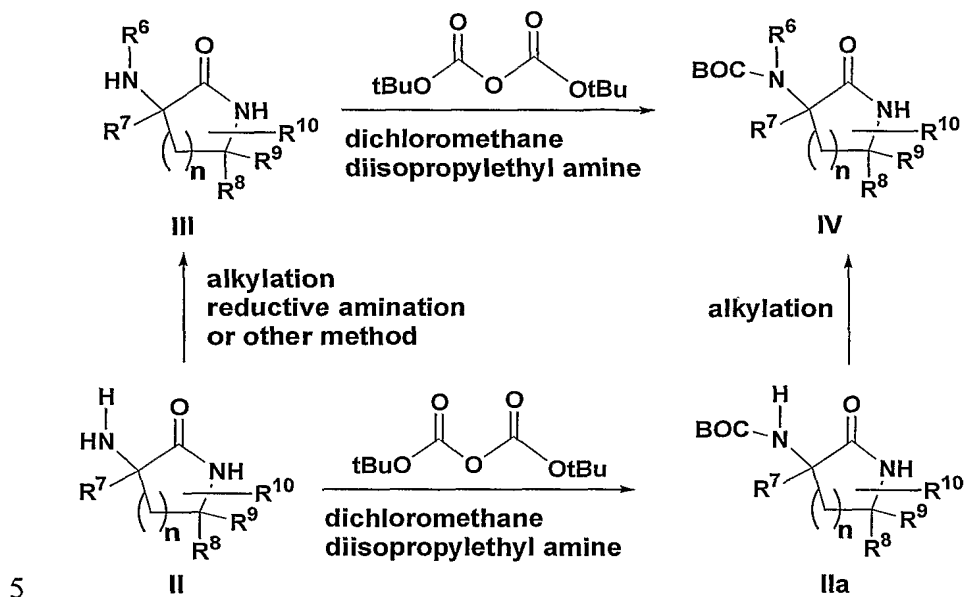
It should be understood that the present invention
25 includes prodrug forms of the compounds of formula I such
as alkylesters of acids or any known prodrugs for lactam
derivatives.

The compounds of the instant invention may, for
example, be in the free or hydrate form, and may be
30 obtained by methods exemplified by the following
descriptions.

The compounds of formula I may be prepared by the
exemplary processes described in the following reaction
schemes. Exemplary reagents and procedures for these
35 reactions appear hereinafter and in the working Examples.

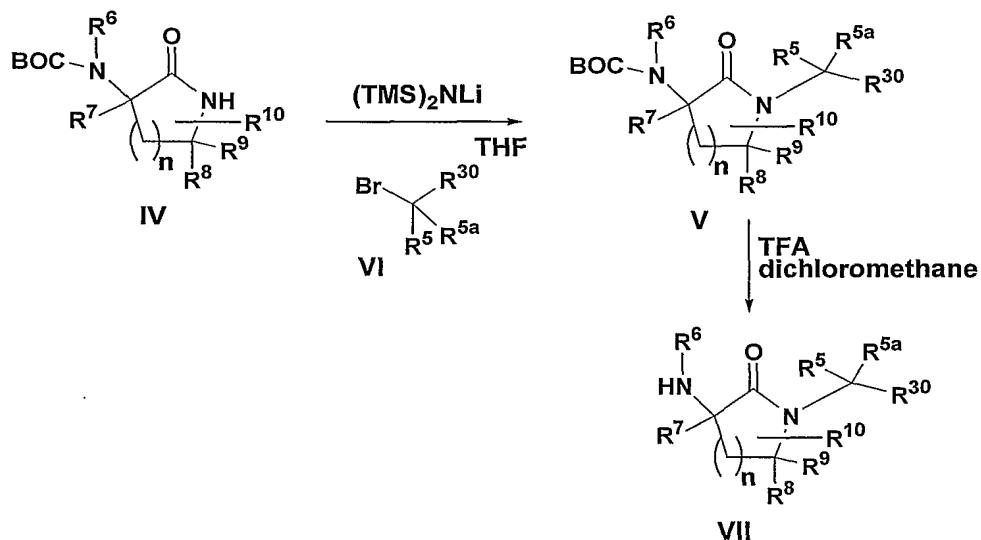
In one method, lactam, II, is converted to IV by
protection followed by substitution (via IIa) or by

substitution followed by protection (via III). The CBZ protecting group or trifluoroacetyl group may be used in place of the BOC-group, for example.



Compound IV is then converted to compound V by alkylation with halide VI. The protecting group is then removed from V by treatment with TFA to provide VII.

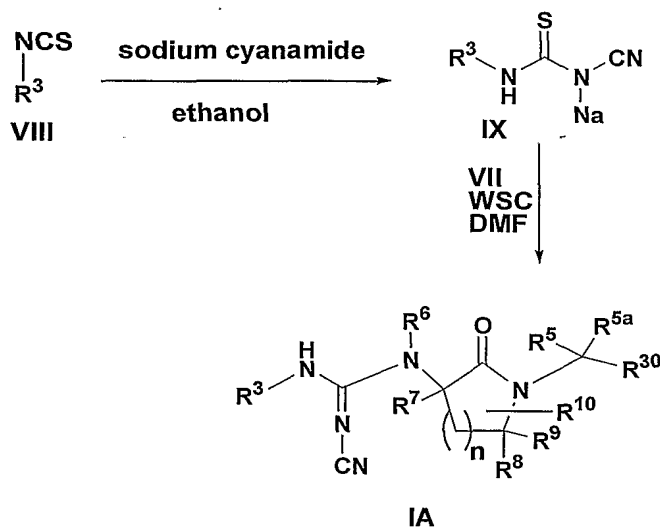
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Compounds of type VII can then be converted to the target compounds as shown in the schemes below. In one

method, an isothiocyanate VIII is converted to compound IX using sodium cyanamide. The salt IX is then coupled to compound VII by using 1-[3-(dimethylamino)propyl]-3-ethyl-carbodiimide (WSC or EDCI) in DMF to yield the

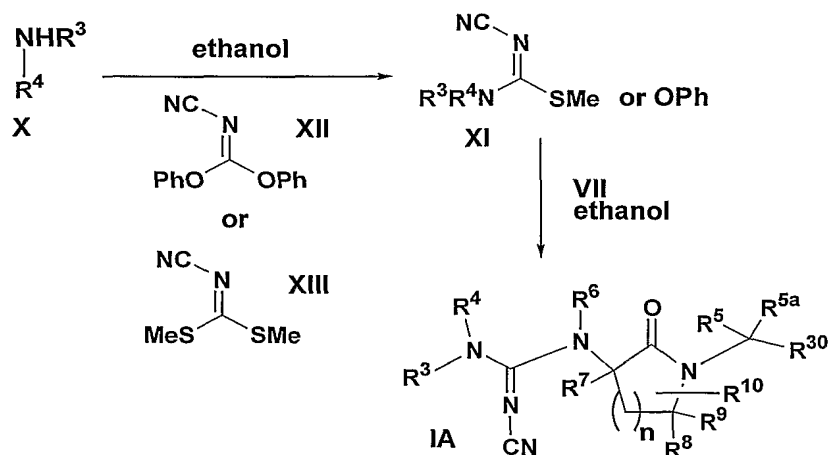
5 targets.



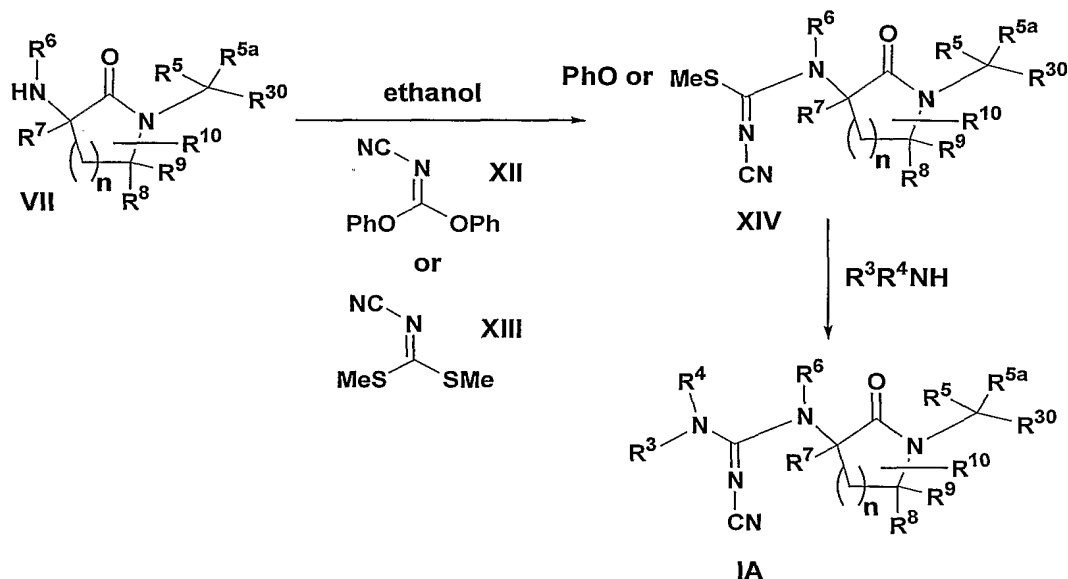
In another method, amine X is converted to intermediate XI by reaction with XII or XIII. Intermediate XI is then converted to target compounds IA by reaction in ethanol, ethyl acetate, DMF and the like. In the case where XI contains the MeS group, a mercury salt (such as mercuric acetate) can be used to speed the

10 reaction.

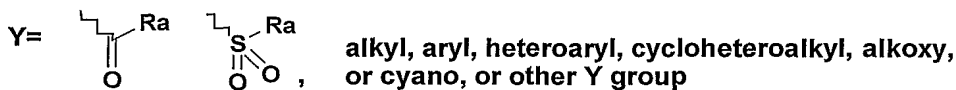
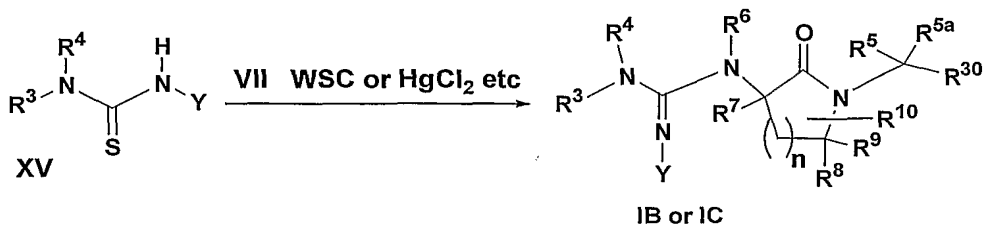
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In another route, compound VII can be reacted with XII or XIII to prepare XIV. Compound XIV is then converted to IA by reaction with an amine in a solvent like acetonitrile or ethanol or DMF.

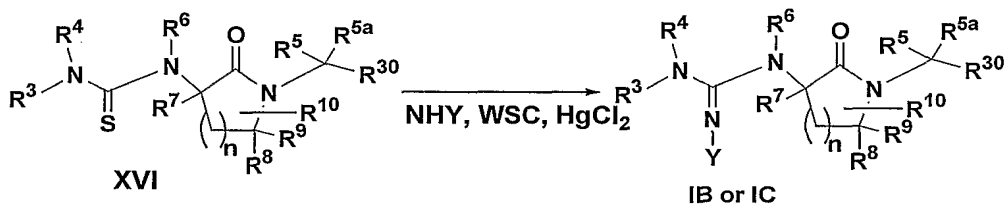


Compounds of the invention of type IB or IC can be prepared from thioureas of type XV. The reaction is carried out in the presence of a coupling agent such as ethyl 3-(dimethylamino)propylcarbodiimide hydrochloride (WSC, EDCI) or the like. Alternatively, the reaction can be carried out in the presence of a mercury salt (such as mercuric chloride, mercuric acetate, mercuric trifluoroacetate, mercuric oxide and the like) or salts of other metals such as silver, cadmium and the like.



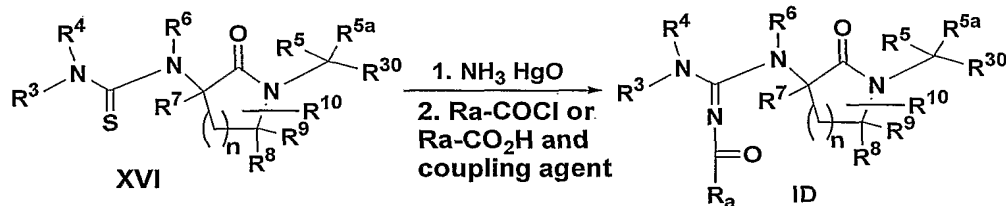
Alternatively, compounds such as IB or IC can be obtained from thioureas of type XVI in a similar manner.

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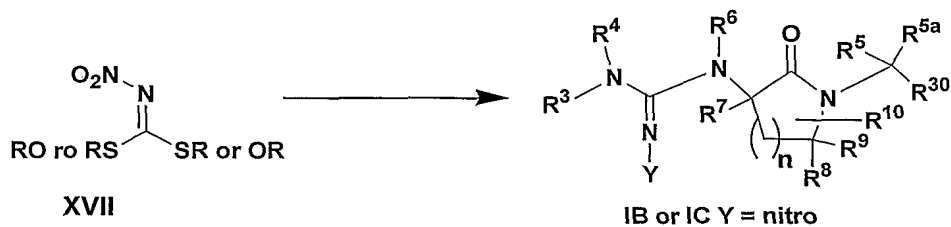


Thioureas of type XV and type XVI can be prepared by methods known in the literature. For example, an isothiocyanate can be reacted with a nitrogen-containing compound in an inert solvent (DMF, acetonitrile, THF, or the like) optionally in the presence of a base such as triethylamine, sodium hydride, tert-butylimino-

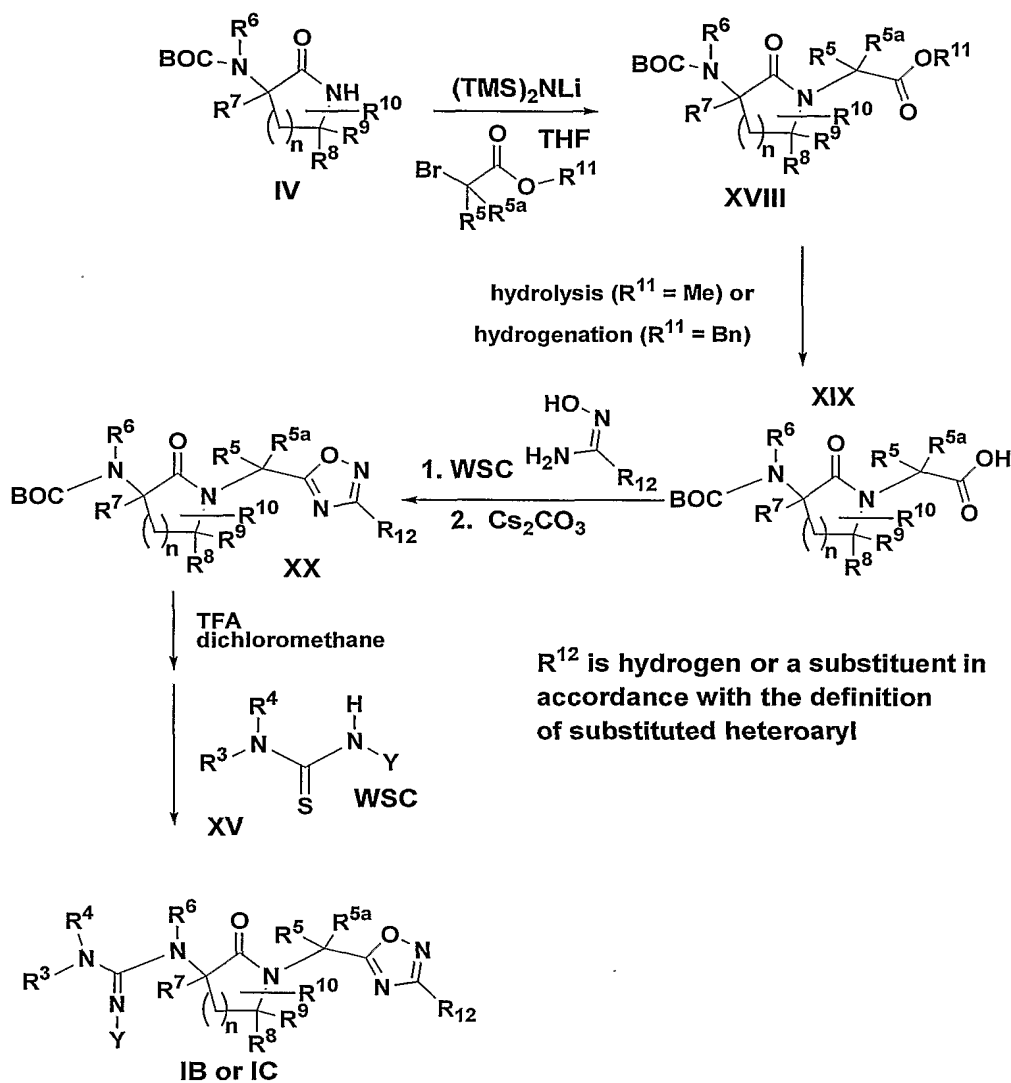
tris(pyrrolidino)phosphorane, Hunig's base, and the like. Alternatively, a multi-step procedure may be used to prepare compounds of type ID (where $\text{Y} = \text{Ra}-\text{C}(\text{O})$).



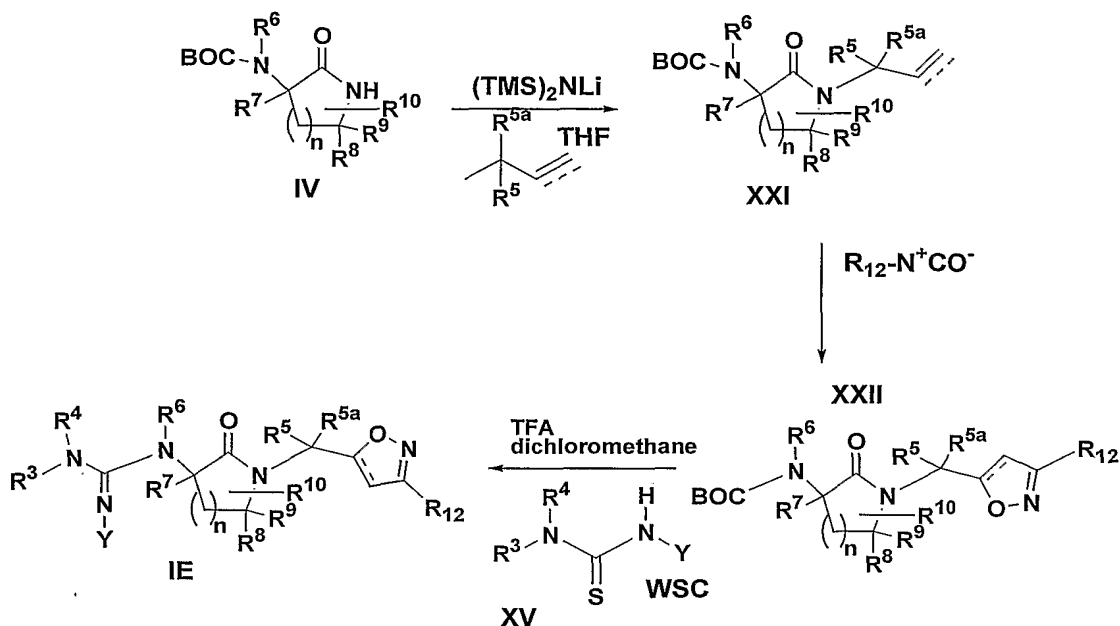
In addition, reagents such as XVII may be used as described above for the synthesis of compounds of type IB and IC



Other target compounds can also be prepared by converting compounds of type IV to esters of type XVIII as described above. These esters can be elaborated in similar manner to provide XIX. Conversion of the ester XVII to the acid XVIII can be accomplished, for example, by hydrogenation if R^{11} is benzyl or by hydrolysis if R^{11} is methyl, ethyl, or benzyl. Coupling and cyclization of XIX provides XX which can be transformed into IB or IC as described above.



Another subset of compounds of type I may be prepared by cycloaddition chemistry using intermediates 5 which are prepared as described above.

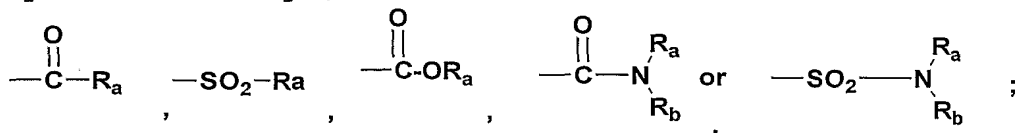


Preferred compounds of this invention are those of formula I including a pharmaceutically acceptable salt thereof wherein:

n is an integer from 1 to 4;

R³ is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, heteroaryl or cycloheteroalkyl;

Y is cyano, nitro, aryl, heteroaryl, cycloheteroalkyl,



R_a and R_b are the same or different and are hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, heteroaryl or cycloheteroalkyl;

R⁴, R⁵, R^{5a}, R⁶, R⁷, R⁸, R⁹ and R¹⁰ are each hydrogen;

R³⁰ is alkyl, substituted alkyl, aryl, C(O)Ra, or heteroaryl and

the configuration at the chiral center is S- (as judged where R⁷ is hydrogen).

The following compounds of formula I including a pharmaceutically acceptable salt thereof are more preferred:

n is 3 or 4, especially 3;

5 R^3 is aryl; especially a substituted benzofuranyl ring;

Y is cyano or $\text{—}\overset{\text{O}}{\parallel}\text{C—R}_a$;

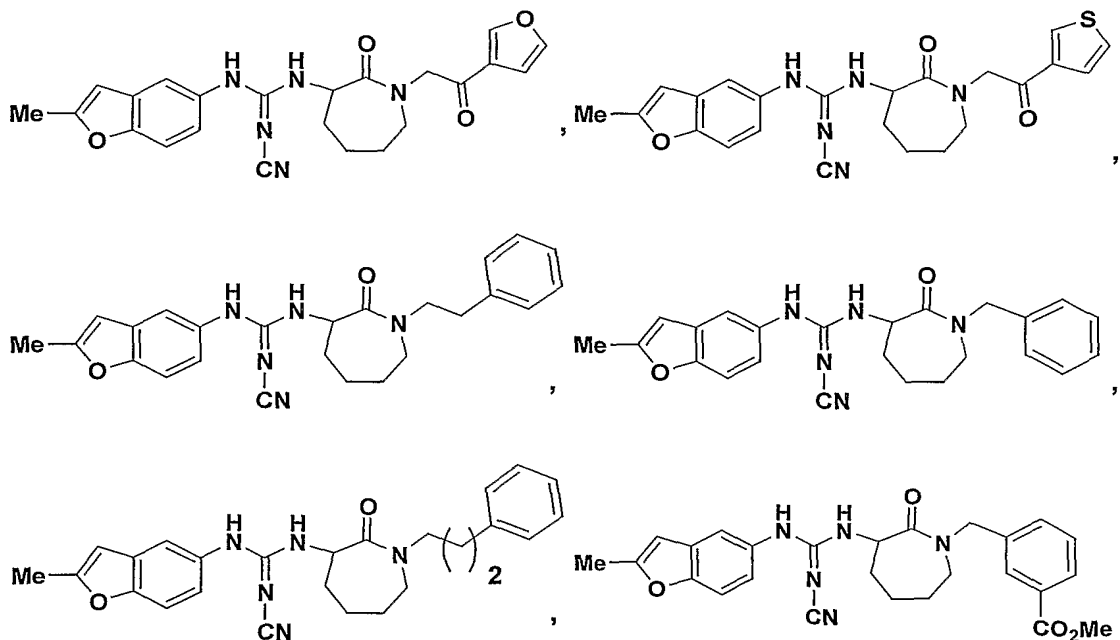
10 R_a and R_b are the same or different and are hydrogen, alkyl, aminocarbonyl, heteroaryl, aryl, or cycloheteroalkyl;

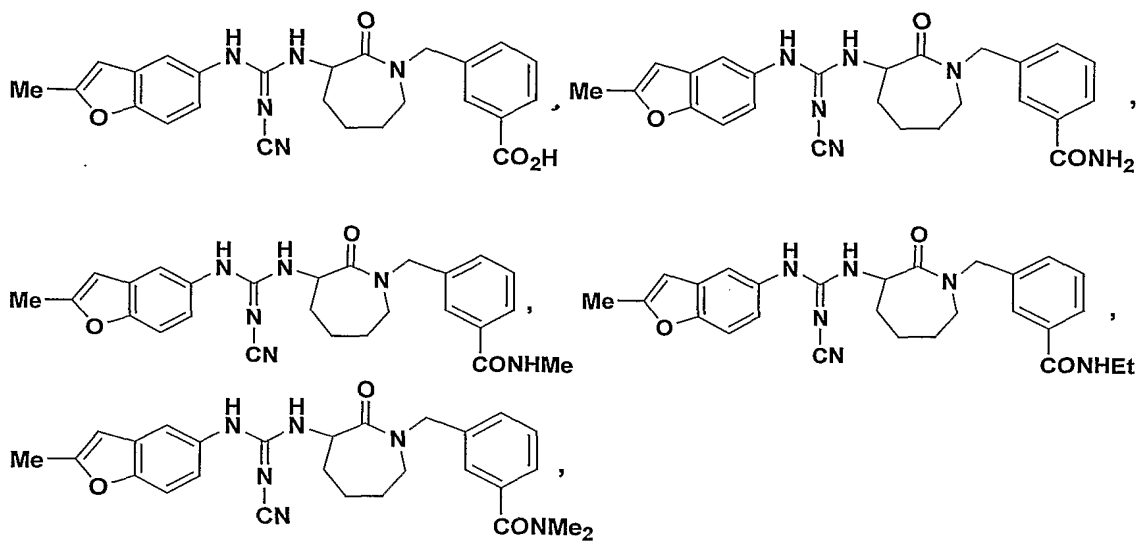
R^4 , R^5 , R^{5a} , R^6 , R^7 , R^8 , R^9 and R^{10} are each hydrogen;

15 R^{30} is aryl, arylalkyl, C(O)-heteroaryl, C(O)aryl, substituted or unsubstituted isoxazol-5-yl, substituted or unsubstituted isoxazolin-5-yl, or substituted or unsubstituted 1,2,4-oxadiazol-5-yl and

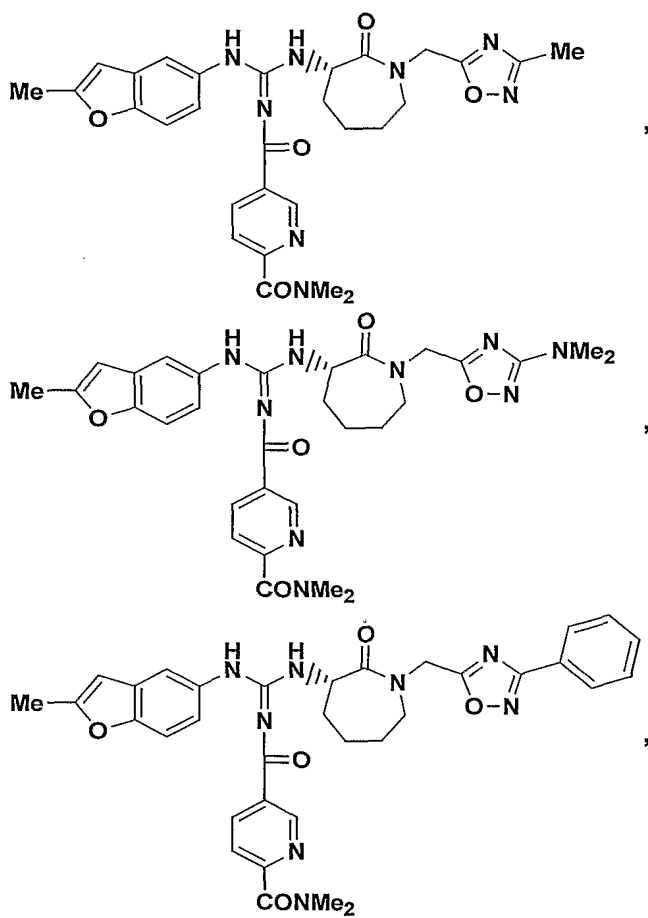
the configuration at the chiral center is S- (as judged where R_i is hydrogen).

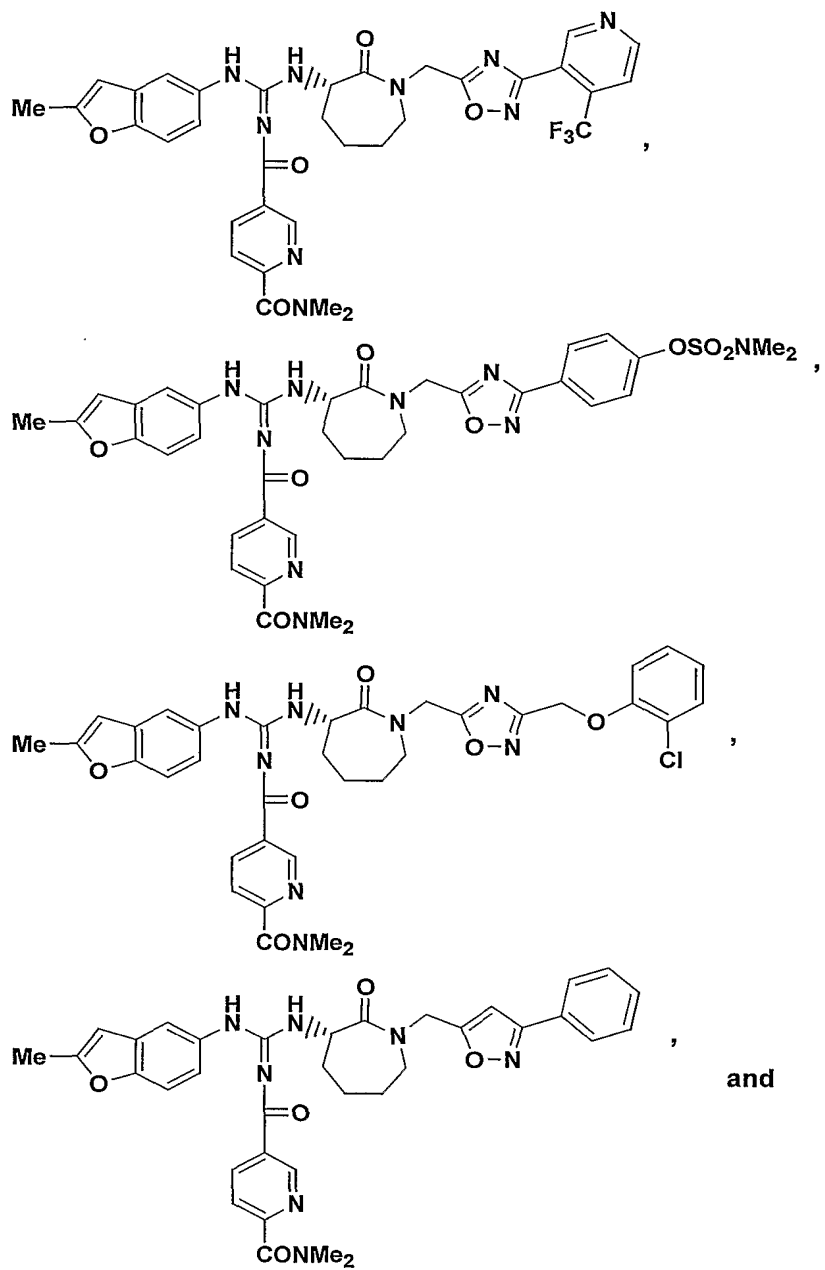
20 The following compounds of formula I including a pharmaceutically acceptable salt thereof are most preferred:



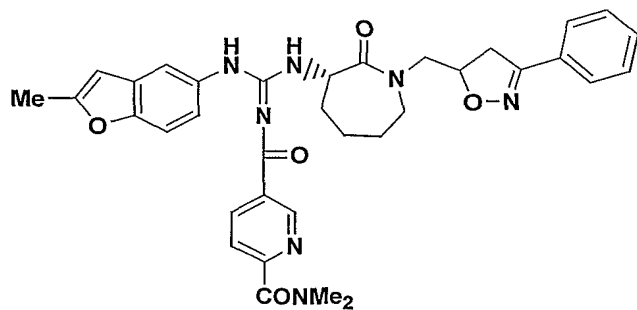


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In the above formulas Me represents methyl and Et represents ethyl, and Ph represents phenyl.

Other methods used in the preparation of compounds
5 of the invention are known to those skilled in the art and are not further described.

The compounds of the present invention are inhibitors of the activated coagulation serine protease known as Factor Xa and thus are useful to maintain the
10 fluidity of blood. Additionally, compounds of the present invention are useful for the treatment or prophylaxis of Factor Xa-associated disorders. As used herein, the term "Factor Xa-associated disorder" refers to any disorder which may be prevented, partially alleviated or cured by
15 the administration of a Factor Xa inhibitor. Thus, the compounds of the present invention are useful in the treatment or prevention of various Factor Xa-associated disorders including: Thrombotic or thromboembolic conditions; acute coronary syndromes (such as coronary
20 artery disease, myocardial infarction (MI), unstable angina and non-Q Wave MI); thromboembolic stroke (such as that resulting from atrial fibrillation or from ventricular mural thrombus (low ejection fraction)); venous thrombosis (including deep vein thrombosis);
25 arterial thrombosis; cerebral thrombosis; pulmonary embolism; cerebral embolism; peripheral occlusive arterial disease (e.g., peripheral arterial disease, intermittent claudication, critical leg ischemia, prevention of amputation, prevention of cardiovascular
30 morbidity such as MI, stroke or death); thromboembolic consequences of surgery, interventional cardiology or immobility; thromboembolic consequences of medication (such as oral contraceptives, hormone replacement and heparin); thrombotic consequences of atherosclerotic
35 vascular disease and atherosclerotic plaque rupture leading to tissue ischemia; prevention of atherosclerotic plaque formation; transplant atherosclerosis;

thromboembolic complications of pregnancy including fetal loss; thromboembolic consequences of thrombophilia (e.g., Factor V Leiden, and homocystinemia); prothrombotic consequences and/or complications of cancer; prevention
5 of thrombosis on artificial surfaces (such as stents, blood oxygenators, shunts, vascular access ports, vascular grafts, artificial valves, etc.); coagulopathies (e.g., disseminated intravascular coagulation (DIC)); coagulation syndromes; vascular remodeling
10 atherosclerosis, restenosis and systemic infection; prevention of metastasis and tumor implantation; diabetic complications including retinopathy, nephropathy and neuropathy; inflammation; ischemia (such as that resulting from vascular occlusion, cerebral infarction, stroke and related cerebral vascular diseases); Kasabach-Merritt syndrome; atrial fibrillation; ventricular enlargement (including dilated cardiac myopathy and heart failure); restenosis (e.g., following arterial injury-induced either endogenously or exogenously).
20 Compounds of the present invention may additionally be useful as diagnostic agents and adjuncts. For example, the present compounds may be useful in maintaining whole and fractionated blood in the fluid phase such as required for analytical and biological
25 testing. In addition, the compounds of the present invention may be useful for maintaining blood vessel patency in conjunction with vascular surgery including bypass grafting, arterial reconstruction, atherectomy, vascular graft and stent patency, organ, tissue and cell
30 implantation and transplantation. In addition, the compounds of the present invention may be useful for maintaining blood vessel patency in conjunction with interventional cardiology or vascular surgery including bypass grafting, arterial reconstruction, atherectomy,
35 vascular graft and stent patency, organ, tissue and cell implantation and transplantation.

The compounds of the present invention may be used in combination with each other, or with other Factor Xa inhibitors. Additionally, the present compounds may be used in combination with one or more of various other
5 therapeutic agents, including: anti-arrythmic agents; anti-hypertensive agents; anti-platelet agents, anti-thrombotic and/or anti-thrombolytic agents; calcium channel blockers (L-type and T-type); cardiac glycosides; diuretics, mineralocorticoid receptor antagonists;
10 phosphodiesterase inhibitors; cholesterol/lipid lowering agents and lipid profile therapies; anti-diabetic agents; anti-depressants; anti-inflammatory agents (steroidal and non-steroidal); anti-osteoporosis agents; hormone replacement therapies; oral contraceptives; anti-
15 coagulants; anti-obesity agents; anti-anxiety agents; anti-proliferative agents; anti-tumor agents; anti-ulcer and gastroesophageal reflux disease agents; growth hormone and/or growth hormone secretagogues; thyroid mimetics (including thyroid receptor antagonist); anti-
20 infective agents; anti-viral agents; anti-bacterial agents; and anti-fungal agents.

Examples of suitable anti-arrythmic agents for use in combination with the present compounds include: Class I agents (such as propafenone); Class II agents (such as
25 carvadiol and propranolol); Class III agents (such as sotalol, dofetilide, amiodarone, azimilide and ibutilide); Class IV agents (such as diltiazem and verapamil); K^+ channel openers such as I_{ACh} inhibitors, and I_{Kur} inhibitors (e.g., compounds such as those disclosed
30 in U.S. Application Serial No. 09/729,731, filed December 5, 2000, WO 01/40231).

Examples of suitable anti-hypertensive agents for use in combination with the compounds of the present invention include: alpha adrenergic blockers; beta
35 adrenergic blockers; calcium channel blockers (e.g. diltiazem, verapamil, nifedipine, amlodipine and mybefradil); diuretics (e.g., chlorothiazide,

hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid, tricyclic, chlorthalidone, furosemide, musolimine, bumetanide, triamtrenene, amiloride, spironolactone); renin inhibitors; ACE inhibitors (e.g., captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril); AT-1 receptor antagonists (e.g., losartan, irbesartan, valsartan); ET receptor antagonists (e.g., sitaxsentan, atrsentan and compounds disclosed in U.S. Patent Nos. 5,612,359 and 6,043,265); Dual ET/AII antagonist (e.g., compounds disclosed in WO 00/01389); neutral endopeptidase (NEP) inhibitors; vasopepsidase inhibitors (dual NEP-ACE inhibitors) (e.g., omapatrilat and gemopatrilat); and nitrates.

Examples of suitable anti-platelet agents for use in combination with the compounds of the present invention include: GPIIb/IIIa blockers (e.g., abciximab, roxifiban, eptifibatide, tirofiban); P2Y₁₂ antagonists (e.g., clopidogrel, ticlopidine, CS-747); thromboxane receptor antagonists (e.g., ifetroban); aspirin; and PDE-III inhibitors (e.g., dipyridamole) with or without aspirin.

Examples of suitable anti-thrombotic and/or anti-thrombolytic agents for use in combination with the compounds of the present invention include: tissue plasminogen activator (natural or recombinant), tenecteplase (TNK), and lanoteplase (nPA); factor VIIa inhibitors; factor Xa inhibitors; thrombin inhibitors (such as hirudin and argatroban); PAI-1 inhibitors (i.e., inactivators of tissue plasminogen activator inhibitors); alpha2-antiplasmin inhibitors; streptokinase, urokinase and prourokinase; and anisoylated plasminogen streptokinase activator complex.

Examples of suitable calcium channel blockers (L-type or T-type) for use in combination with the compounds

of the present invention include diltiazem, verapamil, nifedipine, amlodipine and mybefradil.

Examples of suitable cardiac glycosides for use in combination with the compounds of the present invention
5 include digitalis and ouabain.

Examples of suitable diuretics for use in combination with the compounds of the present invention include: chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide,
10 methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid, tricyclic, chlorthalidone, furosemide, bumetanide, triamterene, amiloride, and spironolactone.

Examples of suitable mineralocorticoid receptor
15 antagonists for use in combination with the compounds of the present invention include spironolactone and eplerenone.

Examples of suitable phosphodiesterase inhibitors for use in combination with the compounds of the present
20 invention include: PDE III inhibitors (such as cilostazol); and PDE V inhibitors (such as sildenafil).

Examples of suitable cholesterol/lipid lowering agents and lipid profile therapies for use in combination with the compounds of the present invention include: HMG-
25 CoA reductase inhibitors (e.g., pravastatin, lovastatin, atorvastatin, simvastatin, NK-104 (a.k.a. itavastatin, or nisvastatin or nisbastatin) and ZD-4522 (a.k.a. rosuvastatin, or atorvastatin or visastatin)); squalene synthetase inhibitors; fibrates; bile acid sequestrants
30 (such as questran); ACAT inhibitors; MTP inhibitors; lipooxygenase inhibitors; cholesterol absorption inhibitors; and cholesterol ester transfer protein inhibitors (e.g., CP-529414).

Examples of suitable anti-diabetic agents for use
35 in combination with the compounds of the present invention include: biguanides (e.g. metformin); glucosidase inhibitors (e.g. acarbose); insulins

(including insulin secretagogues or insulin sensitizers); meglitinides (e.g. repaglinide); sulfonylureas (e.g., glimepiride, glyburide and glipizide); biguanide/glyburide combinations (e.g., Glucovance),
5 thiozolidinediones (e.g. troglitazone, rosiglitazone and pioglitazone), PPAR-alpha agonists, PPAR-gamma agonists, PPAR alpha/gamma dual agonists, SGLT2 inhibitors, inhibitors of fatty acid binding protein (aP2) such as those disclosed in U.S. Serial No. 09/519,079 filed March
10 6, 2000 (attorney docket LA27), glucagon-like peptide-1 (GLP-1), and dipeptidyl peptidase IV (DP4) inhibitors.

Examples of suitable anti-depressant agents for use in combination with the compounds of the present invention include nefazodone and sertraline.

15 Examples of suitable anti-inflammatory agents for use in combination with the compounds of the present invention include: prednisone; dexamethasone; enbrel; protein tyrosine kinase (PTK) inhibitors; cyclooxygenase inhibitors (including NSAIDs, and COX-1 and/or COX-2
20 inhibitors); aspirin; indomethacin; ibuprofen; piroxicam; naproxen; celecoxib; and/or rofecoxib.

Examples of suitable anti-osteoporosis agents for use in combination with the compounds of the present invention include alendronate and raloxifene.

25 Examples of suitable hormone replacement therapies for use in combination with the compounds of the present invention include estrogen (e.g., conjugated estrogens) and estradiol.

30 Examples of suitable anti-coagulants for use in combination with the compounds of the present invention include heparins (e.g., unfractionated and low molecular weight heparins such as enoxaparin and dalteparin).

35 Examples of suitable anti-obesity agents for use in combination with the compounds of the present invention include orlistat and aP2 inhibitors (such as those disclosed in U.S. Serial No. 09/519,079 filed March 6, 2000 (attorney docket LA27)).

Examples of suitable anti-anxiety agents for use in combination with the compounds of the present invention include diazepam, lorazepam, buspirone, and hydroxyzine pamoate.

5 Examples of suitable anti-proliferative agents for use in combination with the compounds of the present invention include cyclosporin A, paclitaxel, FK 506, and adriamycin.

10 Examples of suitable anti-tumor agents for use in combination with the compounds of the present invention include paclitaxel, adriamycin, epithilones, cisplatin, and carboplatin.

15 Examples of suitable anti-ulcer and gastroesophageal reflux disease agents for use in combination with the compounds of the present invention include famotidine, ranitidine, and omeprazole.

20 The various other therapeutic agents described above may be employed in the same dosage form with the compound of formula I or in different dosage forms, in dosages and regimens as generally known in the art or in the PDR.

25 The compounds of the present invention may act in a synergistic fashion with one or more of the above agents to prevent reocclusion following a successful thrombolytic therapy and/or reduce the time to reperfusion. The compounds of the present invention may also allow for reduced doses of the thrombolytic agent to be used and therefore minimize potential hemorrhagic side-effects.

30 The compounds of the present invention may also inhibit other serine proteases, for example, thrombin, Factor VIIa, urokinase-type plasminogen activator (urokinase), tryptase and/or trypsin. As a result, these compounds may additionally be useful as angiogenesis
35 inhibitors in the treatment of cancer, as antiinflammatory agents particularly in the treatment of chronic asthma and in the treatment or prevention of

allergic rhinitis, rheumatoid arthritis, inflammatory bowel disease, psoriasis, and conjunctivitis and in the treatment or prevention of pancreatitis.

5 The compounds of the invention can be administered orally or parenterally such as subcutaneously or intravenously, as well as by nasal application, rectally or sublingually to various mammalian species known to be subject to such maladies, e.g., humans, cats, dogs and the like in an effective amount within the dosage range
10 of about 0.1 to about 100 mg/kg, preferably about 0.2 to about 50 mg/kg and more preferably about 0.5 to about 25 mg/kg (or from about 1 to about 2500 mg, preferably from about 5 to about 2000 mg) on a regimen in single or 2 to 4 divided daily doses.

15 The active substance can be utilized in a composition such as tablet, capsule, solution or suspension or in other type carrier materials such as transdermal devices, iontophoretic devices, rectal suppositories, inhalant devices and the like. The
20 composition or carrier will contain about 5 to about 500 mg per unit of dosage of a compound or mixture of compounds of formulas I, IA., IB, IC and ID. They may be compounded in conventional matter with a physiologically acceptable vehicle or carrier, excipient, binder,
25 preservative, stabilizer, flavor, etc., as called for by accepted pharmaceutical practice.

The following working Examples represent preferred embodiments of the present invention.

30 general experimental and definitions:

TFFH: Tetramethylfluoroformamidinium hexafluorophosphate.

EDCI and WSC: 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride.

35 DMF: N,N-dimethylformamide

HPLC Methods:

Method 1: column- YMC ODS S-5, 4.6 mm x 50 mm; flow- 4
mL/min.; detection- 220 nm; solvent- A- 10% MeOH/water +
0.2% phosphoric acid, B- 90% MeOH/water + 0.2% phosphoric
acid; linear gradient- 0% B to 100% B over 4 min then
5 hold at 100% B for 2 min.

Method 2: identical to method 1 using a Phenom-Luna
(ODS) S-5, 4.6 mm x 50 mm column and with 1 min post-
gradient hold.

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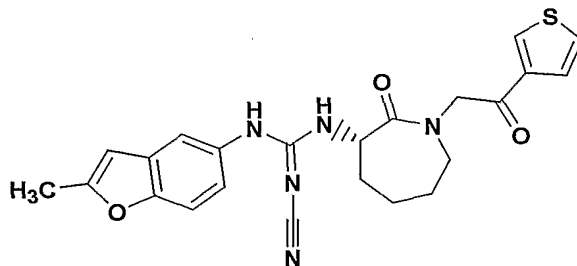
Method 3: column- YMC ODS-A 4.6 X 50 mm I.D. S-3, 120
A; flow- 2.5 mL/min.; detection- 217 nm; solvent- A-
90:10 water:MeOH + 0.2% phosphoric acid, B- 10:90
water:MeOH + 0.2% phosphoric acid; linear gradient- 0% B
15 to 100% B over 8 min then hold at 100 % B for 3 min.

Method 4: column-Phenom-LUNA 4.6x50 mm, S-5; flow- 4
mL/min.; detection- 220 nm; solvent- A- 90:10 H2O:MeOH +
0.2% phosphoric acid, B- 10:90 H2O:MeOH + 0.2% phosphoric
20 acid; linear gradient- 0% B to 100% B over 4 min then
hold at 100 % B for 1 min.

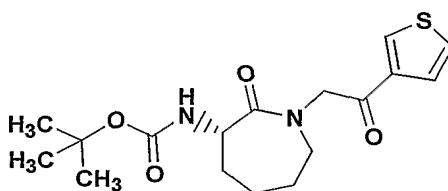
LCMS Conditions:

Method 1: column- YMC ODS S-5, 4.6 mm x 50 mm; flow- 4
25 mL/min.; detection- 220 nm; solvent- A- 10% MeOH/water +
0.1% TFA, B- 90% MeOH/water + 0.1% TFA; linear gradient-
0% B to 100% B over 4 min then hold at 100% B for 1 min.

Method 2: column- YMC ODS S-5, 4.6 x 33 mm; flow- 5
30 mL/min; detection- 220 nm; solvent- A- 10% MeOH/water +
0.1% TFA, B- 90% MeOH/water + 0.1% TFA; linear gradient-
0% B to 100% B over 2 min then hold at 100% B for 1 min.

Example 1

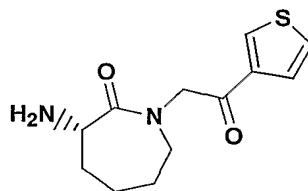
5 Part A:



Lithium hexamethyldisilazide (1M in THF, 8 mL, 8
10 mmol) in tetrahydrofuran (4 mL) was added over 10 min to
a stirring solution of 1,1-dimethylethyl [(3S)-hexahydro-
2-oxo-1H-azepin-3-yl]carbamate (0.92 g, 4.0 mmol) in
tetrahydrofuran (68 mL) under argon. The mixture was
stirred at ambient temperature for 30 min, whereupon 2-
15 bromo-1-(3-thienyl)ethanone (1.24 g, 6.0 mmol) in
tetrahydrofuran (12 mL) was added over 3 min. After
stirring at ambient temperature for 1.5 h, the reaction
was quenched with 5% potassium hydrogensulfate and
transferred to a separatory funnel with ethyl acetate.
20 The mixture was extracted with ethyl acetate, washed with
brine, dried over MgSO_4 and concentrated in vacuo to
afford 2.1 g of crude product. Flash chromatography
(silica, 25 mm dia column, 25% ethyl acetate/hexanes)
afforded part A compound (0.44 g, 31%).

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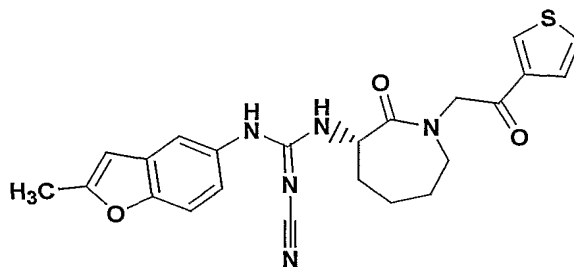
Part B:



5 Trifluoroacetic acid (1.4 g, 0.94 mL, 12 mmol) was added to a solution of part A compound (0.44 g, 1.2 mmol) in dichloromethane (8 mL). After stirring at ambient temperature for 2 h, the reaction was evaporated *in vacuo*. The residue was dissolved in and then evaporated, sequentially, with dichloromethane (2 x 50 mL), methanol (50 mL) and dichloromethane (50 mL). This residue was taken up in methanol and chromatographed on BIORAD AG-50W x 2 (hydrogen form, 9 g, prewashed with 20 mL each of methanol, water, 50% methanol/water). The column was washed with methanol (25 mL), and the compound was then eluted with 2N ammonia in methanol to afford the product as a dark red oil. Flash chromatography (silica, 15 mm dia column, 10% methanol/dichloromethane) of this residue afforded part B compound (0.24 g, 76%) as a yellow oil.

20

Part C:



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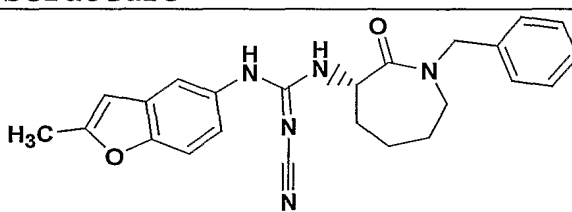
To 2-methyl-5-benzofuranamine (0.22 mmol) in DMF (0.35 mL) was added diphenyl cyanocarbonimidate (0.22 mmol). The mixture heated at 55° C for 30 min. Part B compound (62 mg, 0.24 mmol) was added and the mixture was

stirred at 55°C for 1 day. Flash chromatography of entire reaction mixture (silica, 15 mm dia column, 2% methanol/dichloromethane) afforded the title compound (65 mg, 66% yield); LRMS (ESI, pos. ion spectrum) m/z 450

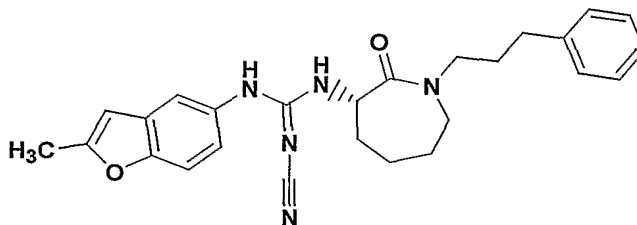
5 (M+H); HPLC (Method 1) t_R 4.0 min.

Example 2

10 Using the procedure described in Example 1 the following was prepared.

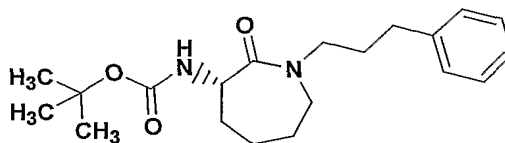
| Example | Structure | Characterization |
|---------|--|---|
| 2 |  | HPLC (method SNB1) t_R 4.2 min LRMS (ESI, pos ion spectrum) m/z 416 (M+H) |

Example 3



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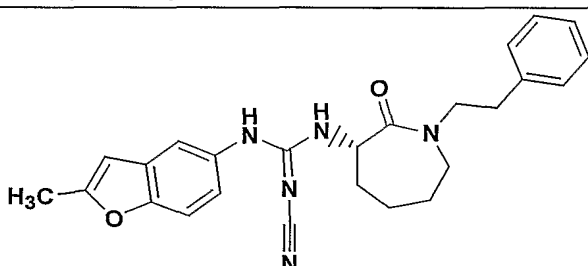
Part A:

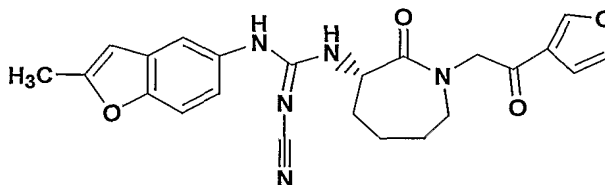


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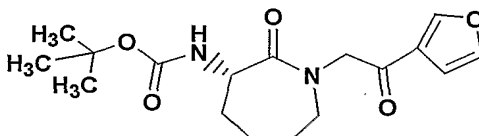
A solution of 1,1-dimethylethyl [(3S)-hexahydro-2-oxo-1H-azepin-3-yl]carbamate (0.35 g, 1.5 mmol) in dimethylformamide (5 mL) was slowly added over 30 min to a suspension of sodium hydride (80% oil dispersion, 90

- mg, 3 mmol) in dimethylformamide (25 mL) stirring at ambient temperature under argon. After stirring at ambient temperature for 30 min, a solution of (3-bromopropyl)benzene (0.45 mL, 3.5 mmol) in
- 5 dimethylformamide (5 mL) was added. After stirring at ambient temperature for 3.5 h, the reaction was quenched with 5% potassium hydrogensulfate and transferred to a separatory funnel with ethyl acetate. Extraction with ethyl acetate, washing with water and 10% aqueous lithium
- 10 chloride, and drying over MgSO_4 afforded 0.6 g of crude product. Flash chromatography (silica, 25 mm dia column, 20% ethyl acetate/hexane) afforded part A compound (0.38 g, 73%).
- 15 Part B: From part A compound the title compound was prepared using procedures described in Example 1: LRMS (ESI, pos. ion spectrum) m/z 444 ($M+H$); HPLC (Method 1) t_R 4.5 min.
- 20 Using the procedure described in Example 2 the following was prepared.

| Example | Structure | Characterization |
|---------|--|--|
| 4 |  | HPLC (method 1) t_R 4.4 min LRMS (ESI, pos ion spectrum) m/z 430 ($M+H$) |

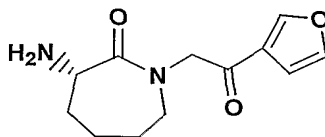
Example 5

5 Part A:



To a 50 mL round bottom flask charged with sodium
 10 hydride (0.15 g, 5.0 mmol) and DMF (10 mL) was added 1,1-
 dimethylethyl [(3S)-hexahydro-2-oxo-1H-azepin-3-
 yl]carbamate (0.57g, 2.5 mmol). The reaction mixture was
 stirred under nitrogen at room temperature for 30 min. A
 solution of 2-bromo-1-(3-furanyl)ethanone (0.9g 5, 5.0
 15 mmol) in DMF (2 mL) was added to the reaction mixture
 slowly. The reaction mixture was stirred at room
 temperature for an additional one hour. The mixture was
 then was concentrated in vacuo. The residue was purified
 by flash chromatography (1:1 hexanes:ethyl acetate) to
 20 provide part A compound (0.19 g, 22% yield).

Part B:



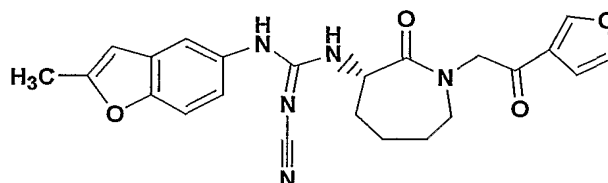
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To a solution of compound part A (0.23g, 1.0 mmol)
 and methylene chloride (2 mL) was added trifluoroacetic
 acid (1.0 mL, 7.0 mmol). The reaction mixture was
 stirred at room temperature for 16 h, and was then
 30 concentrated. The residue was taken up in methanol and

loaded on a column of Biorad AG-50W x 2 (hydrogen form, prewashed with water and methanol). The column was washed with methanol and then eluted with 2 N ammonia in methanol to provide part B compound (0.11 g, 67% yield).

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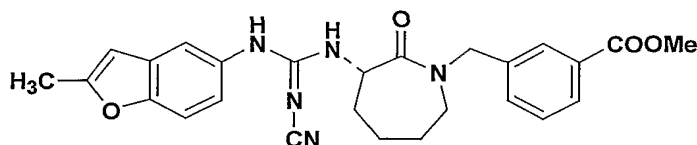
Part C:



To 2-methyl-5-benzofuranamine (0.22 mmol) in DMF (0.35 mL) was added diphenyl cyanocarbonimidate (0.22 mmol). The mixture heated at 55° C for 30 minutes. Part B compound (49 mg, 0.20 mmol) dissolved in DMF (1 mL) was added. The reaction mixture was stirred at 55 °C for 24 hours. The reaction mixture was diluted with ethyl acetate (50 mL). The organic layer was washed with brine (2 x 30 mL), dried over magnesium sulfate and concentrated in vacuo. Flash chromatography (silica gel, 2:1 hexanes/ethyl acetate) provided the title compound (42 mg, 48%) as a white solid: HPLC (method 4) t_R 3.6 min; LCMS (ESI, pos. ion spectrum) m/z 434 (M+H)

20

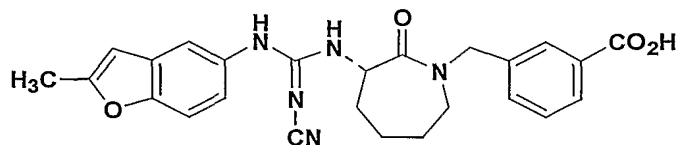
Example 6



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Using the method described in Example 5, the title compound was prepared: HPLC (method 4) t_R 4.0 min; LCMS (ESI, pos. ion spectrum) m/z 474 (M+H)

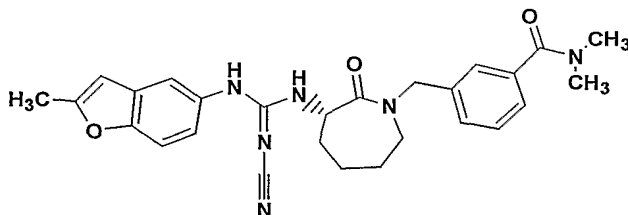
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Example 7

5 The compound of example 6 (510 mg, 1.07 mmol) was dissolved in THF (10 mL) and 8.6 mL of 2.5 M LiOH aqueous solution was added. The reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was concentrated by rotary evaporation and the residue was

10 dissolved in methylene chloride. The organic mixture was extracted with water (2 x 25 mL). The combined aqueous layers were brought to pH 4 with 1 N HCl. The resultant aqueous mixture was then was extracted with ethyl acetate (2 x 25 mL). The combined ethyl acetate extracts were

15 dried over Na₂SO₄ and concentrated to give the title compound (490 mg, 100%): HPLC (method 4) t_R 3.8 min; LCMS (ESI, pos. ion spectrum) m/z 460 (M+H).

Example 8

20 The compound of Example 7 (46 mg, 0.10 mmol) was dissolved in XX mL of DMF, then TFFH (26 mg, 0.10 mmol) and Et₃N (0.020 mL, 0.14 mmol) were added. The reaction mixture was stirred at room temperature for 30 min. Then

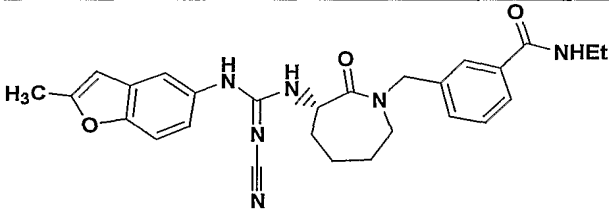
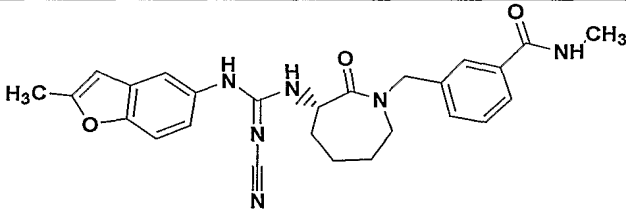
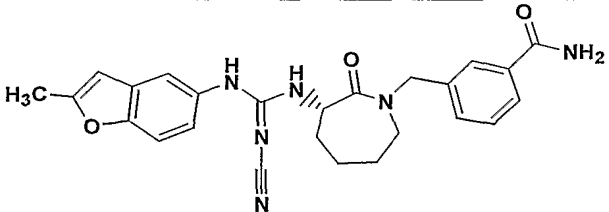
25 2 M dimethyl amine in THF (0.060 mL, 0.12 mmol) was added, and the reaction mixture was continued stirring at room temperature for another 2 hours. The reaction

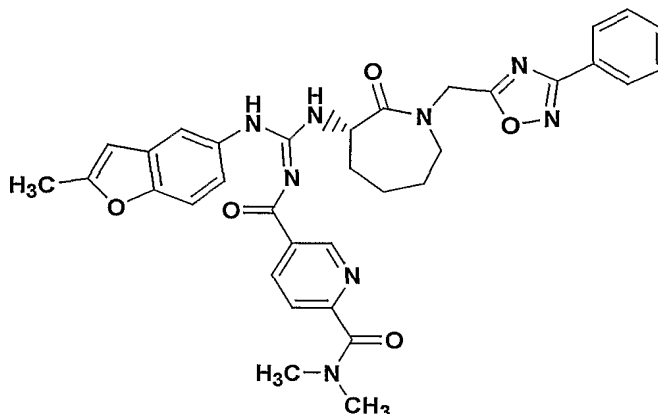
30 mixture was diluted with ethyl acetate (20 mL). The organic solution was washed with brine (2 x 20 mL) and

concentrated. The residue was purified by preparative HPLC (C-18 column; solvent A- 90:10 water:MeOH + 0.2% TFA and solvent B- 10:90 water:MeOH + 0.2% TFA) to provide the title compound (XXX mg, XXX%): HPLC (method 4) t_R 3.6 min; LCMS (ESI, pos. ion spectrum) m/z 487 (M+H).

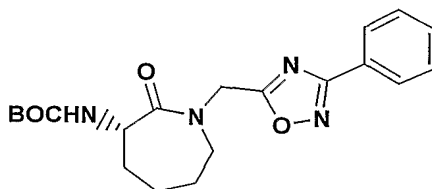
Examples 9-11

Using the procedure described in Example 8, the following were prepared.

| example | structure | characterization |
|---------|--|--|
| 9 |  | HPLC (method 3) t_R 3.7 min LCMS (ESI, pos. ion spectrum) m/z 487 (M+H) |
| 10 |  | HPLC (method 3) t_R 3.6 min LCMS (ESI, pos. ion spectrum) m/z 473 (M+H) |
| 11 |  | HPLC (method 3) t_R = 3.5 min LCMS (ESI, pos. ion spectrum) m/z 459 (M+H) |

Example 12

5 Part A:

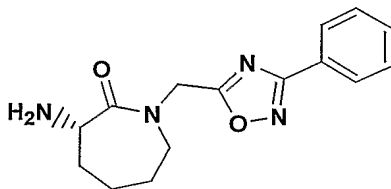


A solution of (3S)-3-[[[1,1-dimethylethoxy)-
 carbonyl]amino]hexahydro-2-oxo-1H-Azepine-1-acetic acid
 10 (0.10 g, 0.35 mmol), 1-[3-(dimethylamino)propyl]-3-
 ethylcarbodiimide hydrochloride (170 mg, 0.58 mmol), and
 1-hydroxybenzotriazole (49 mg, 0.36 mmol) in
 dichloromethane (1.5 mL) and dimethylformamide (0.40 mL)
 was stirred at ambient temperature for 30 min. N-
 15 hydroxybenzenecarboximidamide (48 gm, 0.35 mmol) in
 dichloromethane (0.5 mL) was then added. After stirring
 at ambient temperature for 1.5 h, the reaction was
 transferred to a separatory funnel with dichloromethane
 and 0.1N hydrochloric acid. The mixture was extracted
 20 with dichloromethane (2 x). The combined organic layers
 were washed with saturated sodium bicarbonate and brine,
 dried over magnesium sulfate and concentrated in vacuo to
 afford 0.14 g of crude material.

This residue was then dissolved in tetrahydrofuran
 25 (2.5 mL) and cesium carbonate (0.25 mg, 0.75 mmol) was

added. After stirring at 50°C for 3 h, the reaction was transferred to a separatory funnel with dichloromethane and 0.1 N hydrochloric acid. The mixture was extracted with dichloromethane (2 x). The combined organic layers
5 were washed with saturated sodium bicarbonate and brine, dried over magnesium sulfate and concentrated in vacuo to afford 0.14 g of crude product. Flash chromatography (silica, 15 mm dia column, 35% ethyl acetate/hexane) afforded part A compound (100 mg, 76%): HPLC (Method 1)
10 t_R 3.9 min; LCMS (ESI, pos ion spectrum, method 1) m/z 387 (M+H), t_R 3.80 min.

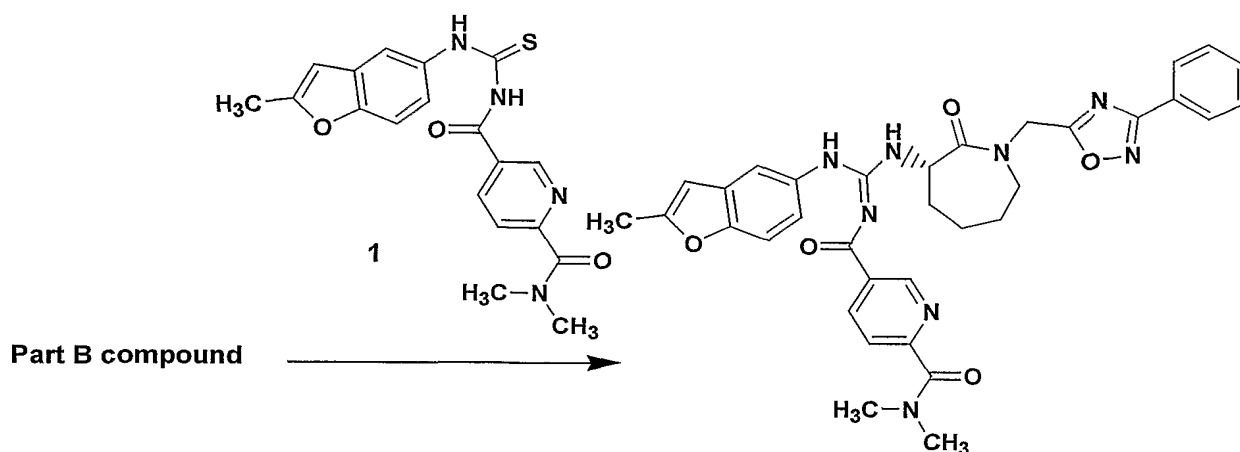
Part B:



15

A solution of part A compound (100 mg, 0.27 mmol) in dichloromethane (0.80 mL) and trifluoroacetic acid (0.40 mL) was stirred at ambient temperature. After 1 h,
20 the reaction was evaporated in vacuo. The residue was coevaporated with dichloromethane (2 x), methanol and dichloromethane to afford crude product (120 mg). This residue was taken up in methanol and added to a column of AG 50W-X2 (200-400 mesh, 3.0 g, prewashed with 8 mL each
25 of methanol, water, and 1/1 methanol/water). The column was washed with methanol (8 mL) and eluted with 2 N ammonia in methanol to afford part B compound (58 mg, 76%): HPLC (Method 1) t_R 2.3 min.

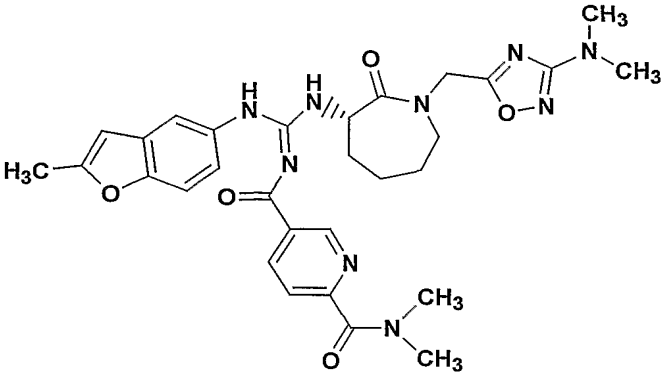
Part C:

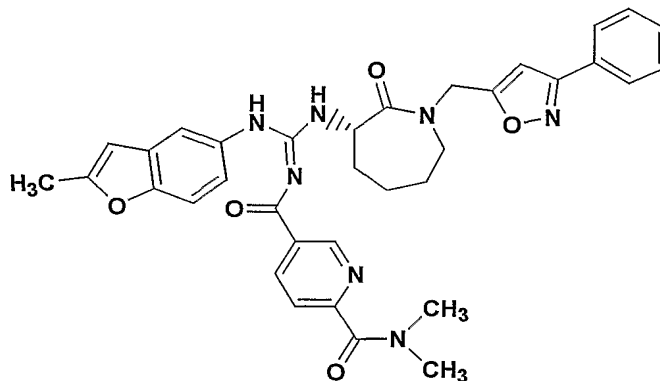


5 Triethylamine (0.088 mL, 0.63 mmol) was added to a
suspension of part B compound (57 mg, 0.20 mmol), **1** (71
mg, 0.18 mmol), and 1-[3-(dimethylamino)propyl]-3-
ethylcarbodiimide hydrochloride (45 mg, 0.23 mmol) in
tetrahydrofuran (0.64 mL). The reaction was stirred at
10 ambient temperature overnight whereupon it was
transferred to a separatory funnel with dichloromethane
and water. The mixture was extracted with
dichloromethane (2 x). The combined organic layers were
dried over magnesium sulfate and concentrated in vacuo to
15 afford crude product. Flash chromatography (silica, 15
mm dia column, 3% methanol/dichloromethane) afforded the
title compound (110 mg, 99%): HPLC (Method 1) t_R 4.31
min, LRMS (ESI, pos ion spectrum) m/z 635 ($M+H$).

Using the procedure described in Example 12 the following compounds were prepared.

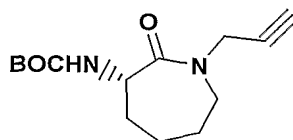
| Example | Structure | Characterization |
|---------|-----------|---|
| 13 | | HPLC (method 1) t_R 4.3 min LRMS (ESI, pos ion spectrum) m/z 699/701 (M+H) |
| 14 | | HPLC (method 1) t_R 4.2 min LRMS (ESI, pos ion spectrum) m/z 758 (M+H) |
| 15 | | HPLC (method 1) t_R 4.1 min LRMS (ESI, pos ion spectrum) m/z 704 (M+H) |
| 16 | | HPLC (method 1) t_R 3.8 min LRMS (ESI, pos ion spectrum) m/z 573 (M+H) |

| | | |
|----|--|--|
| 17 |  | HPLC (method 1) t_R 3.9 min LRMS (ESI, pos ion spectrum) m/z 602 (M+H) |
|----|--|--|

Example 18

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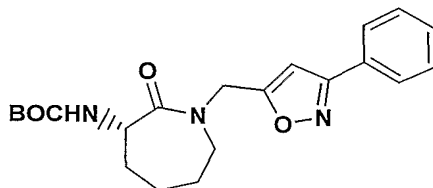
Part A:



- 10 Lithium hexamethyldisilazide (1.0 N in THF, 8.0 mL, 8.0 mmol) in tetrahydrofuran (8 mL) was slowly added over 25 min to a stirring solution of 1,1-dimethylethyl [(3S)-hexahydro-2-oxo-1H-azepin-3-yl]carbamate (0.92 g, 4.0 mmol) in tetrahydrofuran (40 mL) at 0°C under argon.
- 15 After stirring at ambient temperature for 30 min, propargyl bromide (80% wt in toluene, 460 mg, 0.44 mL, 3.9 mmol) in tetrahydrofuran (4 mL) was added. After stirring overnight, the reaction was transferred to a

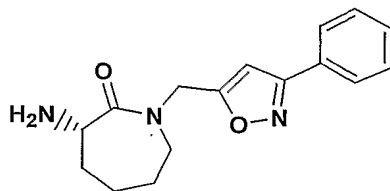
separatory funnel with ethyl acetate and 5% potassium hydrogensulfate. The mixture was extracted with ethyl acetate (2 x). The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated in vacuo to afford 1.5 g of crude product. Flash chromatography (silica, 15 mm dia column, 50% ethyl acetate/hexane) afforded part A compound (0.85 g, 80%): HPLC (Method 1) t_R 3.3 min; LCMS (ESI, pos ion spectrum, method 1) m/z 267 (M+H), t_R 3.1 min.

Part B:



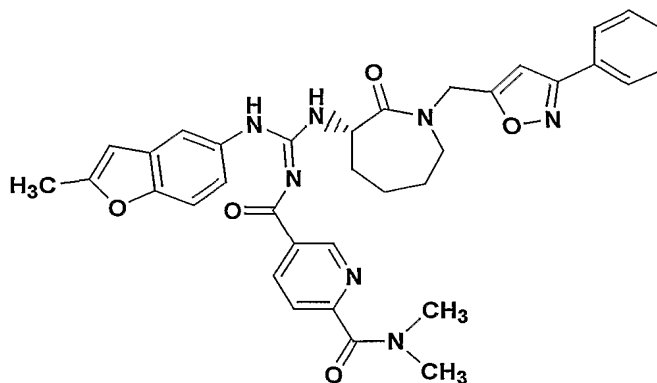
A solution of N-chlorosuccinimide (72 mg, 0.54 mmol), benzaloxime (65 mg, 0.54 mmol), and pyridine (0.27 mL) in dichloromethane (2.0 mL) was refluxed for 1 hour. After cooling the reaction to ambient temperature, part A compound (0.15 g, 0.54 mmol) in dichloromethane (0.5 mL) was added followed by triethylamine (0.54 mL) in dichloromethane (0.25 mL). After refluxing an additional hour, the reaction was transferred to a separatory funnel with dichloromethane, washed with water, and dried over magnesium sulfate to afford 0.25 g of crude product after evaporation of the solvent. Flash chromatography (silica, 15 mm dia column, 20 to 50% ethyl acetate/hexane) afforded part B compound (58 mg, 28%): HPLC (Method 1) t_R 3.9 min.

Part C:



5 A solution of part B compound (58 mg, 0.15 mmol)
in dichloromethane (0.50 mL) and trifluoroacetic acid
(0.25 mL) was stirred at ambient temperature. After 1.5
h, the reaction was evaporated in vacuo. The residue was
coevaporated with dichloromethane (2 x), methanol and
10 dichloromethane to afford crude product. This residue
was taken up in methanol and added to a column of AG 50W-
X2 (200-400 mesh, 1.4 g, prewashed with 5 mL each of
methanol, water, and 1/1 methanol/water). The column was
washed with methanol (5 mL) and eluted with 2 N ammonia
15 in methanol to afford part C compound (34 mg, 80%): HPLC
(Method 1) t_R 2.3 min.

Part D:

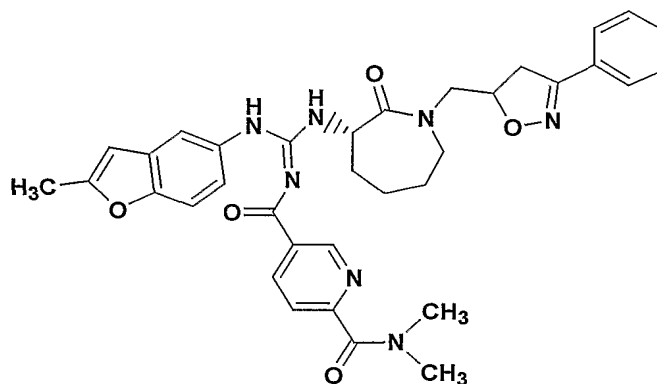


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Triethylamine (0.052 mL, 0.37 mmol) was added to a
suspension of part C compound (34 mg, 0.12 mmol), **1** (42
mg, 0.11 mmol), and 1-[3-(dimethylamino)propyl]-3-
25 ethylcarbodiimide hydrochloride (26 mg, 0.13 mmol) in
tetrahydrofuran (0.40 mL). After stirring at ambient

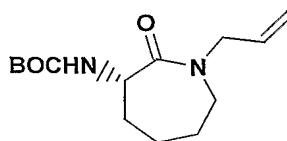
temperature overnight, the reaction was transferred to a separatory funnel with dichloromethane and water. The mixture was extracted with dichloromethane (2 x), dried over magnesium sulfate and concentrated in vacuo to afford the crude product. Flash chromatography (silica, 15 mm dia column, 3% methanol/dichloromethane) afforded the title compound (53 mg, 76%): HPLC (Method 1) t_R 4.2 min; LRMS (ESI, pos ion spectrum) m/z 634 (M+H).

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Example 19

Part A:

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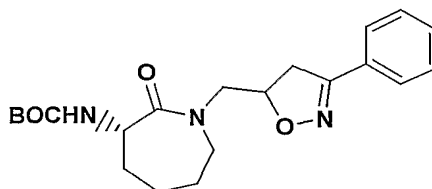


Lithium hexamethyldisilazide (1.0 N in THF, 8.0 mL, 8.0 mmol) in tetrahydrofuran (8 mL) was added over 25 min to a stirring solution of 1,1-dimethylethyl [(3S)-hexahydro-2-oxo-1H-azepin-3-yl]carbamate (0.92 g, 4.0 mmol) in tetrahydrofuran (40 mL) at 0°C under argon. After stirring at ambient temperature for 30 min, allyl bromide (80% wt in toluene, 460 mg, 0.44 mL, 3.9 mmol) in tetrahydrofuran (4 mL) was added. After 2 days, the reaction was transferred to a separatory funnel with ethyl acetate and 5% potassium hydrogensulfate. The mixture was extracted with ethyl acetate (2 x). The

25

combined organic layers were washed with brine, dried over magnesium sulfate and concentrated to afford crude product. Flash chromatography (silica, 25 mm dia column, 25% ethyl acetate/hexane) afforded part A compound (1.0 g, 92%): HPLC (Method 1) t_R 3.5 min; LCMS (ESI, pos ion spectrum, method 1) m/z 269 (M+H), t_R 3.1 min.

Part B:



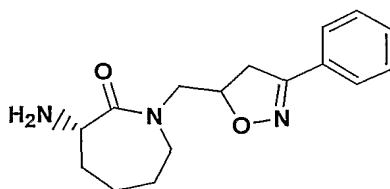
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A solution of N-chlorosuccinimide (68 mg, 0.51 mmol), benzaldoxime (61 mg, 0.51 mmol), and pyridine (0.025 mL) in dichloromethane (2.0 mL) was refluxed for 1 hour. After cooling the reaction to ambient temperature, part A compound (0.14 g, 0.51 mmol) in dichloromethane (0.5 mL) was added followed by triethylamine (0.051 mL) in dichloromethane (0.25 mL). After refluxing an additional hour, the reaction was transferred to a separatory funnel with dichloromethane, washed with water, and dried over magnesium sulfate to afford 0.20 g of crude product after evaporation of the solvent. Flash chromatography (silica, 15 mm dia column, 40% ethyl acetate/hexane) afforded part B compound (120 mg, 61%): HPLC (Method 1) t_R 3.8 min; LCMS (ESI, pos ion spectrum, method 2) m/z 388 (M+H), t_R 1.7 min.

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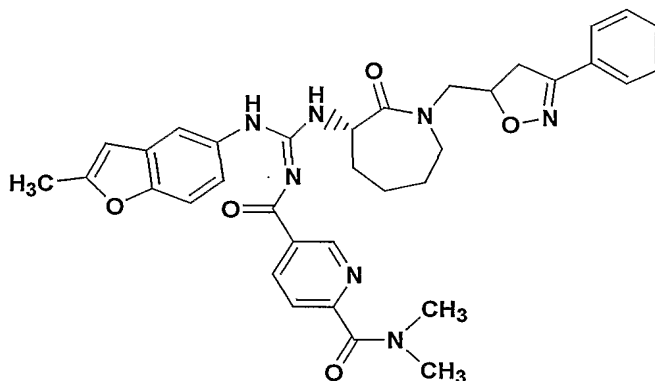
Part C:



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A solution of part B compound (120 mg, 0.30 mmol) in dichloromethane (0.90 mL) and trifluoroacetic acid (0.45 mL) was stirred at ambient temperature. After 2.5 h, the reaction was evaporated in vacuo. The residue was coevaporated with dichloromethane (2 x), methanol and dichloromethane to afford crude product. This residue was then taken up in methanol and added to a column of AG 50W-X2 (200-400 mesh, 3.3 g, prewashed with 9 mL each of methanol, water, and 1/1 methanol/water). The column was washed with methanol (9 mL) and eluted with 2 N ammonia in methanol to afford part C compound (76 mg, 89%): HPLC (Method 1) t_R 2.1 and 2.2 min.

Part D:

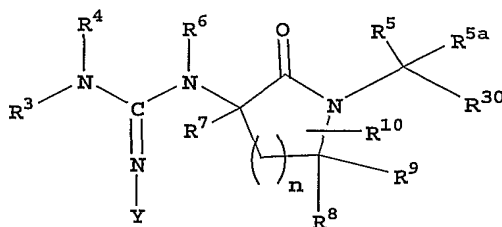


Triethylamine (0.11 mL, 0.80 mmol) was added to a suspension of part C compound (76 mg, 0.26 mmol), **1** (91 mg, 0.24 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (56 mg, 0.28 mmol) in tetrahydrofuran (0.86 mL). After stirring at ambient temperature overnight, the reaction was transferred to a separatory funnel with dichloromethane and water. The mixture was extracted with dichloromethane (2 x). The combined organic layers were dried over magnesium sulfate and concentrated in vacuo to afford crude product. Flash chromatography (silica, 15 mm dia column, 3%

methanol/dichloromethane) afforded the title compound (130 mg, 85%): HPLC (Method 1) t_R 4.2 min; LRMS (ESI, pos ion spectrum) m/z 636 (M+H).

What is claimed is:

1. A compound having the formula

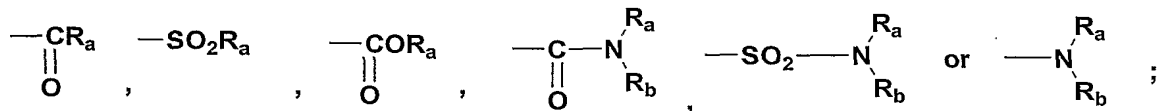


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including a pharmaceutically acceptable salt thereof and all stereoisomers thereof, and prodrugs thereof, wherein:

n is an integer from 1 to 5;

10 Y is selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, cycloalkyl, heteroaryl, cycloheteroalkyl, cyano, nitro, hydroxy, amino, -OR_a, -SR_a,



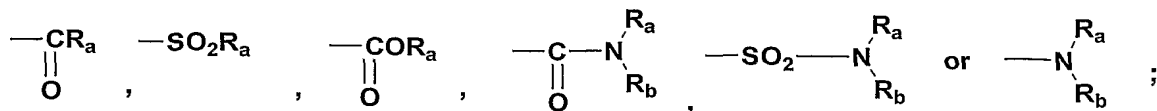
15

R⁴, R⁶, and R⁹ are the same or different and are independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl, cycloheteroalkyl, cycloalkyl, alkylcarbonyl, arylcarbonyl, cycloalkylcarbonyl, substituted alkyl-carbonyl, cycloheteroalkylcarbonyl and heteroarylcarbonyl;

20

R³ is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl, cycloalkyl, cycloheteroalkyl, cyano, nitro, hydroxy, -OR_a, -SR_a,

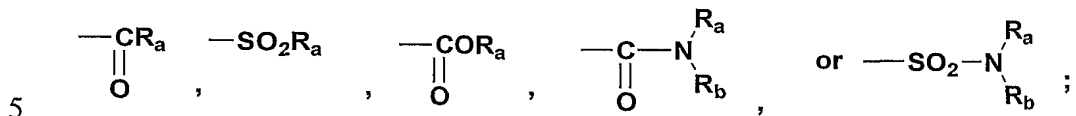
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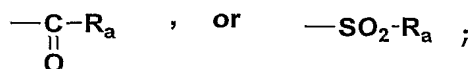
R⁵, R^{5a}, and R⁷ are the same or different and are independently selected from hydrogen, halogen, alkyl,

substituted alkyl, alkenyl, substituted alkenyl, alkynyl,
substituted alkynyl, heteroaryl, cycloalkyl, aryl,
cycloheteroalkyl,



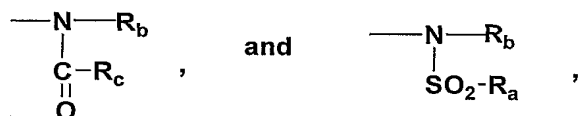
R^{30} is alkyl, substituted alkyl, alkenyl,
substituted alkenyl, alkynyl, substituted alkynyl,
heteroaryl, cycloalkyl, aryl, cycloheteroalkyl,

10



R^{10} is selected from hydrogen, halogen, alkyl,
substituted alkyl, alkenyl, substituted alkenyl, alkynyl,
substituted alkynyl, aryl, heteroaryl, cycloalkyl,
15 alkylcarbonyl, arylcarbonyl, cycloheteroalkyl,
cycloalkylcarbonyl, substituted alkyl-carbonyl,
cycloheteroalkylcarbonyl, heteroarylcarbonyl,

15

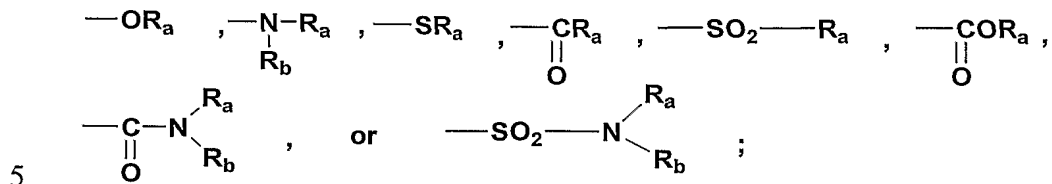


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or when R^9 is hydrogen and R^8 and R^{10} are on adjacent
carbons they join to complete a cycloalkyl or phenyl
ring;

R_a and R_b are the same or different and are
25 independently selected from hydrogen, alkyl, substituted
alkyl, alkenyl, substituted alkenyl, alkynyl, substituted
alkynyl, aryl, heteroaryl, cycloheteroalkyl, cycloalkyl,
alkylcarbonyl, arylcarbonyl, cycloalkylcarbonyl,
substituted alkyl-carbonyl, cycloheteroalkylcarbonyl,
30 heteroarylcarbonyl, aminocarbonyl, alkylaminocarbonyl and
dialkylaminocarbonyl;

R_C is hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, heteroaryl, cycloalkyl, cycloheteroaryl,



and wherein R³ and R⁴ and/or R_a and R_b can be taken together with the nitrogen to which they are attached to form a cycloheteroalkyl ring or a heteroaryl ring;

10 R³ and Y can be taken together to form a
 heteroaryl ring;

R³ or R⁴ or Y can form a ring with R⁶ which can be a cycloheteroalkyl or a heteroaryl ring;

R⁵ and R^{5a} can be taken together to the carbon to
15 which they are attached to form a cycloalkyl ring, a
heteroaryl ring or a cycloheteroalkyl ring; and

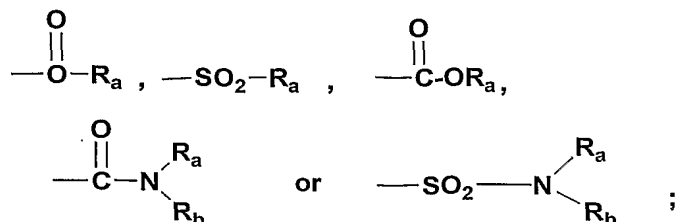
where one or more of R^3 R^4 or R^6 are H, then double bond isomers are possible.

20 2. A compound of Claim 1 wherein:

n is an integer from 1 to 4;

R³ is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, heteroaryl or cycloheteroalkyl;

25 Y is cyano, nitro, aryl, heteroaryl,
cycloheteroalkyl,



R_a and R_b are the same or different and are hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, heteroaryl or cycloheteroalkyl;

R^4 , R^5 , R^{5a} , R^6 , R^7 , R^8 , R^9 and R^{10} are each hydrogen;

5 R^{30} is alkyl, substituted alkyl, $-C(O)R_a$, or heteroaryl; and

the configuration at the chiral center is S-(as judged where R^7 is hydrogen).

10 3. A compound of Claim 2 wherein:

n is 3 or 4;

R^3 is aryl;

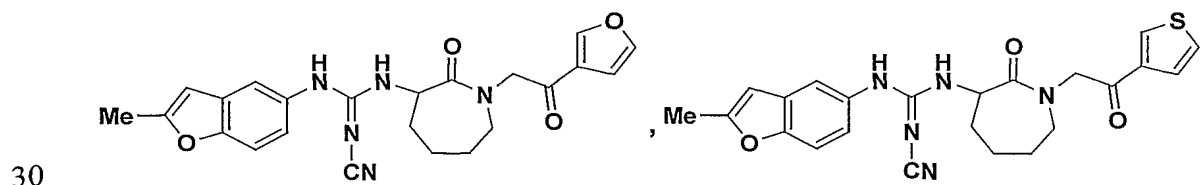
Y is cyano or $\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}-\text{R}_a \end{array}$;

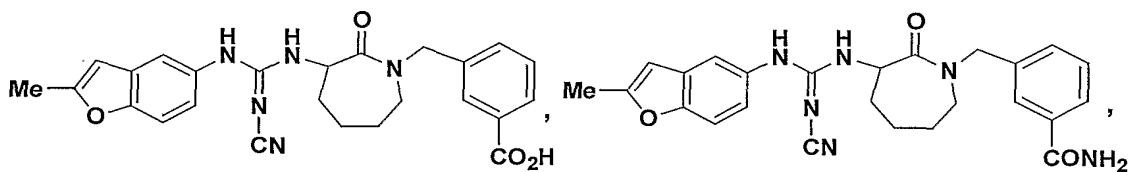
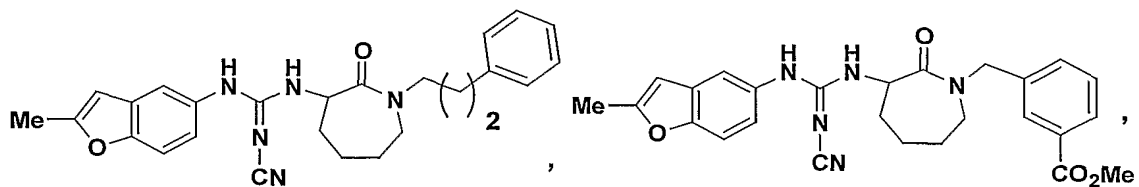
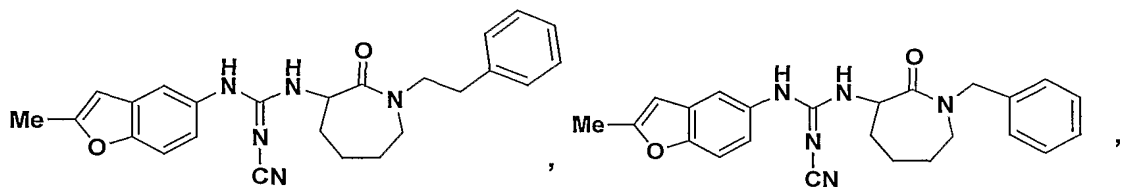
15 R_a and R_b are the same or different and are hydrogen, alkyl, aminocarbonyl, heteroaryl, aryl or cycloheteroalkyl;

R^{30} is aryl, arylalkyl, $-C(O)$ -heteroaryl, $-C(O)$ aryl, substituted or unsubstituted isoxazol-5-yl, substituted or unsubstituted isoxazoline-5-yl, or
20 substituted or unsubstituted 1,2,4-oxadiazol-5-yl-; and
the configuration at the chiral center is S-(as judged where R_7 is hydrogen).

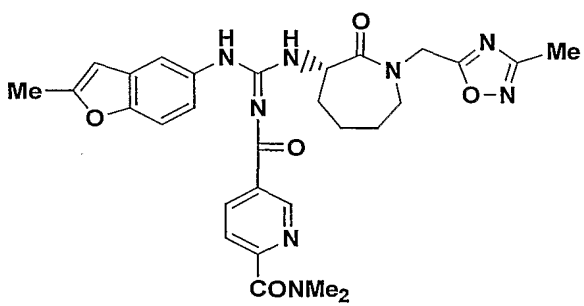
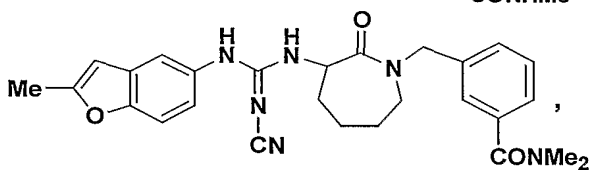
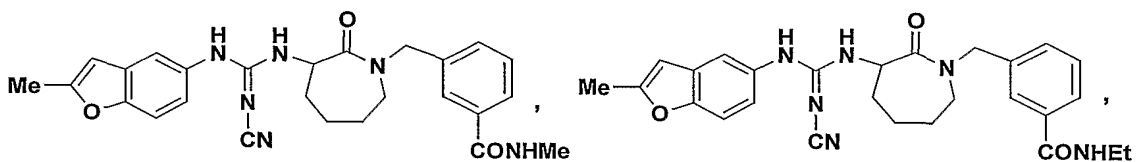
25 4. The compound of Claim 3 wherein n is 3; and R^3 is substituted benzofuranyl.

5. A compound of Claim 1 including a pharmaceutically acceptable salt thereof of the formula:

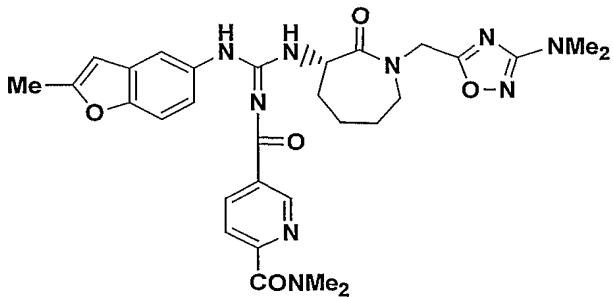


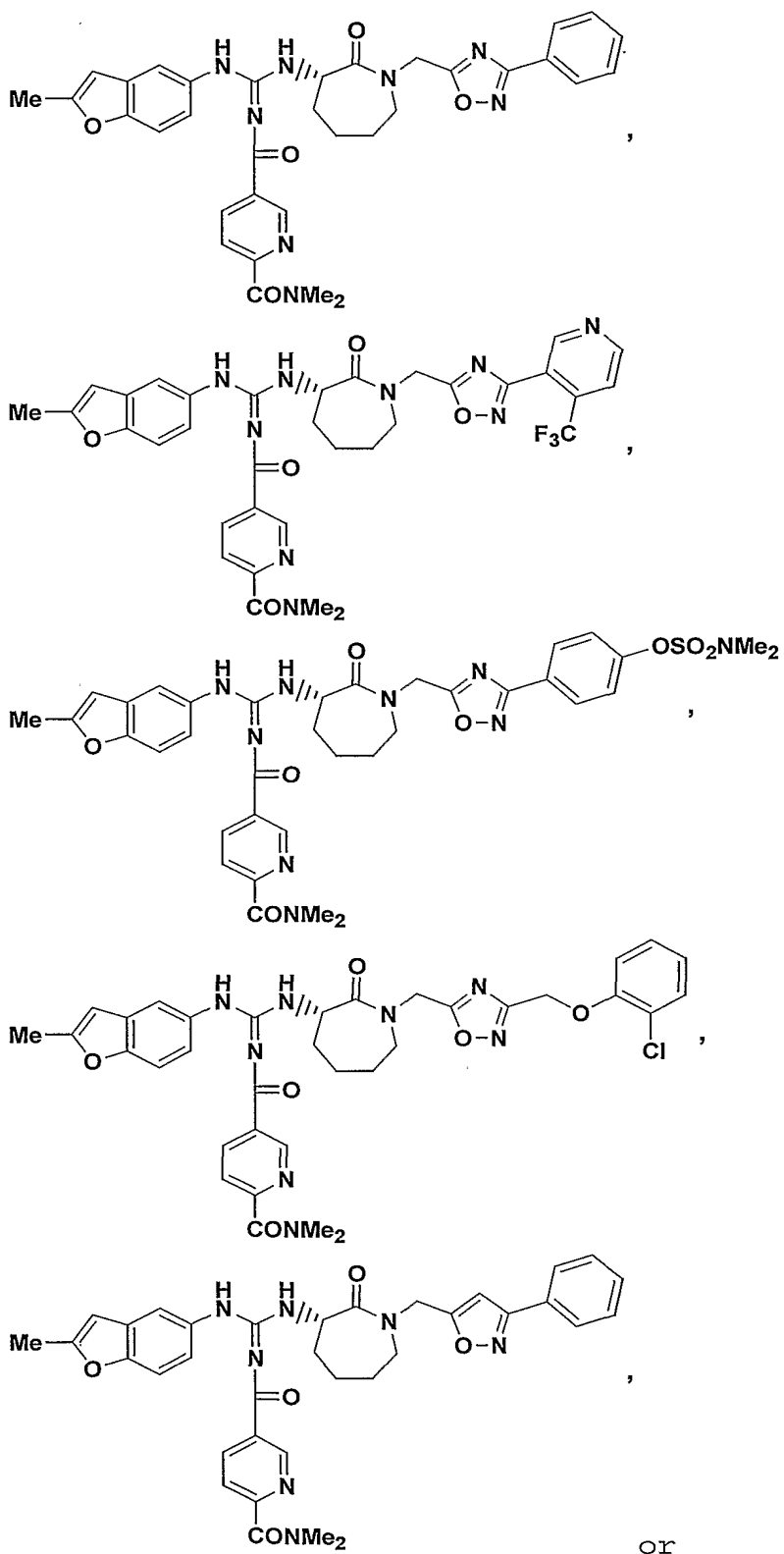


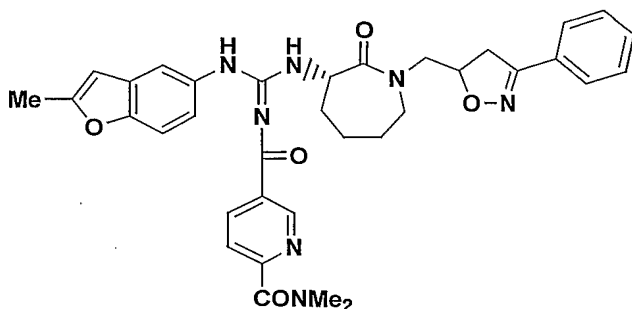
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10







6. A pharmaceutical composition comprising a compound as defined in Claim 1 and a pharmaceutically acceptable carrier therefor.

7. The pharmaceutical composition of claim 6 further comprising at least one additional therapeutic agent selected from anti-arrythmic agents, anti-hypertensive agents, anti-platelet agents, anti-thrombotic agents, anti-thrombolytic agents, calcium channel blockers, cardiac glycosides, diuretics, mineralocorticoid receptor antagonists, phosphodiesterase inhibitors, lipid lowering agents and lipid profile therapies, anti-diabetic agents, anti-depressants, anti-inflammatory agents, anti-osteoporosous agents, hormone replacement therapies, and oral contraceptives.

8. The pharmaceutical composition of claim 7 wherein the additional therapeutic agent is an anti-arrythmic agent selected from sotalol, dofetilide, amiodarone, azimilide, ibutilide, diltiazem and verapamil, K⁺ channel openers, an anti-hypertensive agent selected from ACE inhibitors, AT-1 receptor antagonists, ET receptor antagonists, dual ET/AII receptor antagonists, and vasopeptidase inhibitors, an antiplatelet agent selected from GPIIb/IIIa blockers, P2Y₁₂ antagonists, thromboxane receptor antagonists, and aspirin, an anti-thrombotic or anti-thrombolytic agent selected from thrombin inhibitors, alpha2-antiplasmin inhibitors, streptokinase, urokinase, and prourokinase,

an anti-diabetic agent selected from biguanides,
sulfonylureas, biguanide/glyburide combinations, aP2
inhibitors, and DP4 inhibitors, or an anti-inflammatory
agent selected from cyclooxygenase inhibitors and
5 aspirin.

9. A method of treating a Factor Xa-associated
disorder comprising administering an effective amount of
at least one compound of claim 1 to a patient in need
10 thereof.

10. The method of claim 9 wherein the Factor Xa-
associated disorder is an acute coronary syndrome
selected from myocardial infarction, unstable angina and
15 non-Q Wave MI, thromembolic stroke, venous thrombosis,
pulmonary embolism, peripheral occlusive consequences of
surgery, interventional cardiology or immobility, the
development of thrombosis on artificial surfaces, the
thrombotic consequences of atherosclerotic vascular
20 disease and/or atherosclerotic plaque rupture,
coagulopathy including disseminated intravascular
coagulation, and the thromboembolic consequences of
thrombophilia.

25

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/23932

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D405/14 C07D409/14 C07D405/12 C07D413/14 A61K31/55
 A61P7/02 A61P9/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | <p>DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; HAGISHITA, SANJI ET AL: "Preparation of novel benzolactam derivatives as neuropeptide antagonists and medicinal compositions comprising them" retrieved from STN Database accession no. 129:260474 XP002184808 CAS RN: 211760-38-2; 211760-64-4; 211760-67-7; 211761-08-9; 211761-09-0; 211761-10-3; 211761-11-4; 211761-12-5; 211761-13-6; 211761-14-7; 211761-15-8; 211761-16-9; 213664-57-4 abstract -& WO 98 41510 A (SHIONOGI & CO., LTD., JAPAN) 24 September 1998 (1998-09-24)</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p> | 1, 10 |

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

5 December 2001

Date of mailing of the international search report

21.12.2001

Name and mailing address of the ISA

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 Fax: (+31-70) 340-3016

Authorized officer

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INTERNATIONAL SEARCH REPORT

In International Application No

PCT/US 01/23932

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | <p>DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; HAGISHITA, SANJI ET AL: "New benzolactam derivatives and medicinal compositions containing the same" retrieved from STN Database accession no. 129:189245 XP002184809 CAS RN: 211760-38-2; 211760-64-4; 211760-67-7; 211760-69-9; 211761-08-9; 211761-09-0; 211761-10-3; 211761-11-4; 211761-12-5; 211761-13-6; 211761-14-7; 211761-15-8; 211761-16-9; 211761-18-1 211761-19-2; 211761-20-5; 211761-21-6; 211761-22-7; 211761-23-8; 211761-24-9; 211761-37-4; 211761-43-2; 211761-44-3; 211761-45-4; 211761-46-5; 211761-47-6 abstract -& WO 98 35941 A (SHIONOGI & CO., LTD., JAPAN) 20 August 1998 (1998-08-20)</p> | 1,10 |
| X | <p>MURAKAMI, YASUSHI ET AL: "1,3-Disubstituted benzazepines as novel, potent, selective neuropeptide Y Y1 receptor antagonists" J. MED. CHEM. (1999), 42(14), 2621-2632 , XP002184807 abstract column 1 examples 41A-41E; table 2</p> | 1,10 |
| X | <p>DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MURAKAMI, YASUSHI ET AL: "1,3-disubstituted benzazepines as neuropeptide Y Y1 receptor antagonists" retrieved from STN Database accession no. 131:299361 XP002184810 CAS RN: 211760-67-7; 21161-08-9; 211761-090; 211761-11-4; 211761-13-3; 211761-14-7; 211761-15-8 abstract & BIOORG. MED. CHEM. (1999), 7(8), 1703-1714 ,</p> | 1,10 |
| P,X | <p>WO 00 47207 A (SQUIBB BRISTOL MYERS CO) 17 August 2000 (2000-08-17) the whole document page 1 -page 4 page 20 -page 26 claims 17-21</p> | 1-4,6-10 |

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INTERNATIONAL SEARCH REPORT

In tional Application No

PCT/US 01/23932

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| A | US 6 063 794 A (ZHU BING-YAN ET AL) 16 May 2000 (2000-05-16) column 16 -column 18 example 7 claims 24-30 ----- | 1,6-10 |

INTERNATIONAL SEARCH REPORT
information on patent family members

In International Application No
PCT/US 01/23932

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
|---|---|---------------------|---|--|
| WO 9841510 | A | 24-09-1998 | WO 9841510 A1 | 24-09-1998 |
| WO 9835941 | A | 20-08-1998 | AU 5880498 A WO 9835941 A1 | 08-09-1998 20-08-1998 |
| WO 0047207 | A | 17-08-2000 | AU 3588700 A EP 1156803 A1 WO 0047207 A1 US 6297233 B1 | 29-08-2000 28-11-2001 17-08-2000 02-10-2001 |
| US 6063794 | A | 16-05-2000 | AU 4900397 A WO 9816524 A1 EP 0939758 A1 | 11-05-1998 23-04-1998 08-09-1999 |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/23932

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 9 and 10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-10 (all partially)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-10 (all partially)

The scope of claims 1-10, in as far as the expression "prodrugs" (see claim 1, page 52, line 7) is concerned, is so unclear (Article 6 PCT) that a meaningful International Search is impossible with regard to this expression.

Nevertheless, the search was complete for compounds of Formula I of claim 1 as well as alkylesters of acids of said compounds (see page 13, line 26).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.